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ENDOMETRIOSIS AND PREGNANCY*

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ENDOMETRIOSIS as a cause of pelvic disease in women has, in recent years, received increasing attention in medical literature. The published reports indicate that the disease is one of the common indications for pelvic surgery.

Sampson[27] described endometriosis as "the presence of ectopic tissue which possesses the histologic structure and function of the uterine mucosa." He states, "It also includes the abnormal conditions which may result not only from the invasion of organs and other structures by this tissue, but also from its relation to menstruation." He divides the disease into two main groups: (1) direct or internal endometriosis when the ectopic mucosa, usually situated in either the uterine or tubal walls, is continuous with the mucosa lining these organs; (2) indirect or external endometriosis when the ectopic mucosa has the same histologic structure as that in the internal type, but is not continuous with normally situated Müllerian mucosa.

A review of the literature on endometriosis (Table I) reveals extensive investigation of this subject by many workers since Cullen[6] in 1895 reported a case of adenomyoma of the uterus, and Russell[24] in 1898 reported a case of aberrant portions of Müllerian duct found in an ovary. The publication of the first of Sampson's[26] classic articles, read before this Society in 1921, intensified the investigation of endometriosis, particularly its histogenesis. That phase of the subject is beyond the scope of this paper and needs no discussion at this time.

In most of the published papers on endometriosis the possibility of pregnancy in young women after a conservative operation is noted but not stressed. Occasionally the occurrence of pregnancy after operation is briefly mentioned. However, Wharton,[33] Beecham,[1, 3] Meigs,[17, 18] Schmitz,[28] Greenblatt,[10] and others have emphasized the importance of conservative surgery whenever possible in women in the child-bearing age. Novak[20] referred to many patients who had complete relief of symptoms after a conservative operation for endometriosis.

TABLE I. Résumé of Thirteen Cases of Endometriosis With Pregnancy. Twelve of These Followed Conservative Surgery

CASE NO.	AGE	FORMER PREG-NANCIES	OPERATION PERFORMED	INTERVAL BEFORE PREGNANCY	CONDITION OF BABY	SUBSEQUENT HEALTH OF MOTHER
1	25	0	Removal of cysts from both ovaries; uterus suspended	7 years (cesarean section)	Normal 2,551 grams	Good; menses irregular; uterus retrodisplaced third degree
2	25	1 normal 1 abortion	Dilatation of cervix; curettage; laparotomy; myomectomy	Aborted 5 months later; 8 weeks pregnant		Good; uterus normal
3	23	2 normal	Left salpingo-oophorectomy; uterine suspension	3 years	Normal 3,572 grams	Good; uterus normal
4	29	0	Left tube and ovary removed	8 months (cesarean section) / 5 years later (cesarean section)	Normal 3,401 grams / Normal 3,090 grams	Good; uterus normal
5	25	0	Adhesions freed; uterus and ovaries replaced in normal position; uterus suspended	3 years / 2 years later (low forceps)	Normal 3,401 grams / Normal 3,430 grams	Good; uterus retrodisplaced third degree; two pregnancies
6	30	1 normal 1 abortion	Left ovary removed; half right ovary resected; Fallopian tubes freed; uterus suspended	4 years	Normal 2,806 grams	Good; uterus normal
7	29	0	Adhesions separated; uterus replaced anterior; left ovary and tube removed	5 months later aborted at 8 weeks		Good
8	29	1 abortion	Adhesions freed; left ovary removed; cyst evacuated	4 months (midforceps)	Normal 3,600 grams	Dysmenorrhea; uterus enlarged; adenomyosis suspended
9	21	0	Adhesions to left ovary freed; uterus suspended	Soon after husband's return from war	Normal 3,770 grams	Good; uterus normal; slight dysmenorrhea
10	24	0	Half each ovary resected; uterus suspended	6 months (low forceps)	Normal 3,373 grams	Good; uterus normal; left ovary enlarged
11	36	0	Endometriosis diagnosed at time of cesarean section		Normal 3,175 grams	Good; has remained well
12	33	0	Adhesions of right ovary and tube freed; left oophorectomy	1 year	Normal 3,657 grams	Good; uterus normal
13	23	0	Most of right ovary removed	2½ years / 1 year	Normal 3,316 grams / Normal 3,515 grams	Good; uterus normal position and size

He mentioned two patients seen in one year in whom unilateral cysts were removed. Pregnancy followed in both cases before the recurrence of symptoms necessitating another operation. Dannreuther[7] had follow-up studies made of twenty young women in whom the child-bearing function had been preserved. He found that two still had moderate pelvic pain and two had been delivered at term, one eighteen months and the other two years after operation. Four of the patients were unmarried.

Although endometriosis is usually considered as a disease occurring in women over 30 years of age, the disease is being reported with increasing frequency in younger women. Meigs claimed that it usually occurs after the age of 26. Holmes[12] reported that 2.5 per cent of his patients with endometriosis were between 20 and 23 years of age, and 8.7 per cent were under 28 years of age, while 51.2 per cent were between 29 and 38 years old. Fallon,[9] in 1946, reported that 4 per cent of his 225 patients with external endometriosis were under 20 years of age and one of these was only 13 years old. A 16-year-old patient reported by McDonald[16] had three endometrial cysts in the posterior vaginal vault two years after the onset of menses. This girl had a double uterus and only one cavity communicated with the vagina.

The increasing recognition of endometriosis in women during the child-bearing age, particularly in young women, necessitates a careful investigation of the possibilities, and also the dangers, of conservative treatment of the disease in women during this period, particularly in those who have no children. Schmitz,[28] in 1947, reported 57 patients with endometriosis treated by surgery. In 47 of the patients conservative surgery was the treatment used. Twenty-five patients in this group were completely relieved of their symptoms and nine conceived and bore eleven infants.

Adenomyosis as a cause of rupture of the pregnant uterus was reported by Stone[31] in 1937. He referred to a similar case reported by Richardson in 1919. Sackett,[25] in 1941, reported a case in which adenomyosis seemed to be the cause of an atony of the uterus and a severe hemorrhage which necessitated hysterectomy following cesarean section.

Recently two significant papers on endometriosis and its effect on pregnancy have been published. The first was by Scott[29] in 1944. He reported two cases in which severe acute symptoms resulting from endometriosis necessitated a laparotomy during the pregnancy. He collected 23 cases of external endometriosis and pregnancy in which the age of the patients was known and added his own two cases, and found the average age was 31.5 years. Of seventeen patients in whom the parity was known, six were pregnant for the first time. Scott also collected twelve cases of internal endometriosis and pregnancy in which the age of the patients was given and found it averaged 36.1 years. In ten patients whose parity was given, four were primigravidas.

The second paper, by Lock,[15] in 1946, reported the case of a 28-year-old white woman who had a spontaneous abortion in 1940. Subsequently she had increasing dysmenorrhea and was operated upon in January, 1943. The left tube and ovary were removed and a cystic cavity in the right ovary was evacuated. Because of an adenomyosis, a fundectomy was done and approximately two-thirds of the corpus of the uterus was removed. Two years later this patient, after an easy labor, was delivered vaginally of a living female child weighing 2,780 grams.

Lock also reported a second case of extensive adenomyosis of the uterus in a patient who, after a labor of six hours, delivered spontaneously a male child weighing 3,010 grams. This patient lost less than 100 c.c. of blood following delivery of the baby.

Recently, Beecham at the Temple University Hospital delivered by cesarean section a normal, living child from a private patient 29 years old in whom extensive pelvic endometriosis had been diagnosed in 1944. In 1946 she had a laparotomy with lysis of adhesions, bilateral resection of cysts from both ovaries, a Baldy-Webster suspension of the uterus, and appendectomy. Two years later she was delivered by cesarean section, had only slight pelvic adhesions, and her convalescence was uneventful.

Scott and TeLinde,[30] in a study of endometriosis not yet published, report a follow-up of sixty-four patients with endometriosis in whom the child-bearing function was preserved at laparotomy. Twenty-six patients had thirty-eight pregnancies following operation. Twenty patients had one or more term pregnancies. Three patients had abortions and three were pregnant when last examined.

The use of radium in the treatment of endometriosis was advocated by Branch[4] in 1946. He stated that complete cure will follow either surgical removal of the ectopic endometrial tissue, or destruction or removal of all ovarian tissue. The latter is to be avoided in women of child-bearing age. Sometimes the former method may be employed without loss of the reproductive function. However, he described three collected cases in which radium had been successfully used against the affected area in the rectovaginal septum; in two of these patients temporary amenorrhea was followed by pregnancy. He reported a personally observed case in an unmarried woman, aged 24 years. who suffered menorrhagia and rectal bleeding at the time of menstruation. A diagnosis of endometriosis of the rectovaginal septum was made and through a suprapubic incision a hard mass was removed by electrosurgical cutting and coagulating current. Drainage was established in the vagina. Two months later the mass had regained its size and it was decided to use irradiation, which had been successfully employed by Griffith in 1913 and by Vignes in 1939. Menstruation was restored 13 days later. The woman married a few months afterwards and eight months after the operation she became pregnant. A normal baby was delivered by cesarean section. Two years later she aborted at the second month of pregnancy. Two years later she was delivered of a second normal child by cesarean section. No signs of endometriosis were noted at any time. This method has not been used in our practice.

The association of endometriosis and sterility has been reported by many observers. In a small group of private patients with endometriosis in whom we were able to preserve the child-bearing function, pregnancy often occurred a few months after the operation. A follow-up of these patients revealed that they frequently remained symptom free after delivery and in a few a second pregnancy occurred.

We present thirteen cases of pregnancy (Table I) in which external endometriosis was proved by operation, either before or during gestation. These are all private patients and they have been personally observed over periods of from several months to eighteen years. Most of the patients were operated upon and then delivered by the same physician. This is admittedly a small group of patients, but the results emphasize the fact that pregnancy with delivery of a normal child can follow conservative surgical treatment of patients with endometriosis.

CASE 1.—A 25-year-old white woman was first examined in September, 1931. She had been married for two years and had never been pregnant. Her chief complaint was dyspareunia. Examination was essentially negative except for pelvic findings which revealed

a small vagina, a normal cervix, and a small, firm, retrodisplaced second degree and fixed uterus. After rest and treatment with vaginal tampons and warm saline douches her symptoms subsided. One year later the dyspareunia recurred and she had severe dysmenorrhae. At this time, two small, dark, bluish implants appeared in the vaginal vault.

In February, 1933, at operation, the uterus was found to be retrodisplaced and bound down by adhesions also involving the ovaries. Endometrial cysts were resected from both ovaries, the uterus was suspended, and the appendix was removed. After operation her condition improved; the menses were irregular but not painful and she remained symptom free.

In 1941 she was pregnant and had a central placenta previa. She was delivered by cesarean section and had an uneventful convalescence. The baby weighed 2,551 grams and remained in good condition.

This patient, when examined in 1946, was in good condition but her menses were irregular. The uterus was retrodisplaced third degree, about normal in size and fixed; the pelvis otherwise was normal.

CASE 2.—A 25-year-old white woman was first examined in March, 1934. Her chief complaint was pregnancy. She had been married two years, and the menses had been regular every twenty-eight days with slight dysmenorrhea until Jan. 10, 1934. Pelvic examination revealed that the uterus was in an anterior position, soft, and symmetrically enlarged to the size of a six weeks' pregnancy. She had no other complaints and the history and physical examination were normal. Her pregnancy was uneventful and she was delivered at term, with low forceps, after a labor of thirteen hours. The baby was alive and normal and remained in good condition. The mother's convalescence was normal.

Six years later, in 1940, she had a spontaneous abortion at the eighth week of pregnancy. In February, 1946, she complained of sterility of five years' duration. Pelvic examination revealed a small intramural fibroid in the posterior wall of the uterus near the fundus. A dilatation of the cervix and curettage of the uterus were performed together with a laparotomy, appendectomy, and myomectomy. The uterus was in an anterior position, and both ovaries and both Fallopian tubes appeared to be normal. There were several dark, bluish, endometrial implants on the anterior surface of the uterus. Her convalescence was uneventful.

Her menses were regular until May, 1946. In July she aborted spontaneously at the eighth week of pregnancy and was later curetted. The uterus has remained in an anterior position and she is in good condition.

CASE 3.—A 23-year-old white woman was first examined June 28, 1935. She had been married two years, and complained since her marriage of severe dysmenorrhea during the first two days of her menses. She was about two months pregnant. The fundus of the uterus was soft and a little enlarged. It was retrodisplaced third degree, but easily replaced in an anterior position. Her physical condition was otherwise normal. Her pregnancy was normal and she delivered spontaneously at term after an easy labor of five hours. The baby was alive and normal.

A second pregnancy in 1940 was uneventful and she delivered spontaneously after a labor of five hours. The baby was alive and normal. Six weeks after delivery the uterus was retrodisplaced third degree but it was easily replaced in an anterior position and she wore a Smith pessary for six weeks.

In 1944 she was operated upon by a surgeon in another hospital for a chocolate cyst of the left ovary. The posterior cul-de-sac was obliterated by adhesions associated with endometriosis. A left salpingo-oophorectomy, uterine suspension (Olshausen's) and appendectomy were performed.

She was examined in our office in September, 1947. At that time she had not menstruated since June 25, 1947, and the uterus was in an anterior position, soft, and symmetrically enlarged to the size of a three months' pregnancy. She remained in good condition and was again delivered at term, after a labor of four hours. The baby was alive, normal, and weighed 3,572 grams. Her convalescence was uneventful.

CASE 4.—A 29-year-old white woman was first examined in May, 1946. She had been married for six weeks and requested contraceptive advice. The past history was negative. Menses had commenced at the age of 13 years, and were regular every twenty-eight days, duration three days, with moderate discomfort. Physical examination was nonrevealing, except that the uterus was retrodisplaced second degree and the mobility was limited. A small cystic mass 4 cm. in diameter was noted in the left side of the pelvis.

Two months later she had missed a menstrual period and the cystic mass in the left side of the pelvis had increased in size. The uterus was soft and seemed to be slightly enlarged. At operation the left ovary was found to be bound down by adhesions to the omentum, the posterior wall of the broad ligament, and to the uterus. The ovary was 6 to 8 cm. in diameter and contained a chocolate cyst. The left Fallopian tube was densely adherent to the cyst wall and it was necessary to remove both the left tube and ovary. After the adhesions were separated, the uterus was lifted out of the pelvis. It was soft and a little enlarged. A few endometrial implants were seen in the posterior cul-de-sac.

She had an uneventful pregnancy and eight months later she was delivered by cesarean section because of a generally contracted pelvis. The baby was alive and normal and weighed 3,401 grams.

This patient had a second pregnancy five years later. Her prenatal course was normal and she was again delivered by section. The baby was alive and normal and weighed 6 pounds and 13 ounces. The mother's convalescence was uneventful, and she has remained well.

CASE 5.—A 25-year-old white woman, who had never been pregnant, was first examined in March, 1939. She had been married for four months and complained of dysmenorrhea. Menses were regular every twenty-eight days, duration six days. Physical examination was negative. The uterus was normal in size but retrodisplaced third degree and fixed. She had considerable pelvic tenderness. When operated upon in May, 1941, the uterus was retrodisplaced and bound down by adhesions but normal in size. Both ovaries were prolapsed into the cul-de-sac and bound down by adhesions. The adhesions were separated and the uterus and ovaries replaced in a normal position. The uterus was then suspended. There were several small, dark, bluish, endometrial implants in the posterior cul-de-sac and along the posterior surface of the uterus. She had some discomfort after operation, but recovered normally.

In 1944 she had an uneventful pregnancy, and was delivered with low forceps, after a labor of seventeen hours. The baby was alive and in good condition and weighed 3,401 grams.

She had another uneventful pregnancy in 1946. After an easy labor of nine hours, a normal living child was delivered with low forceps. He weighed 3,430 grams.

The patient was last examined in October, 1948. She had no complaints and her condition was good except for a third degree retrodisplacement of the uterus which did not cause any discomfort.

CASE 6.—A 30-year-old white woman was first examined in February, 1940. She had been married for four years. The former history was noncontributory except that she usually had dysmenorrhea and had never been pregnant prior to the last menses in the middle of October, 1940. Pelvic examination revealed that the uterus was in an anterior position, soft, and symmetrically enlarged to the size of a three months' pregnancy. The other pelvic structures were normal. Her pregnancy was normal and she was delivered at term, with outlet forceps, after an easy labor of five hours. The baby was alive and normal and weighed 2,806 grams. The mother's convalescence was uneventful.

Three years later the patient had a spontaneous abortion at the eighth week of pregnancy. Following a dilatation and curettage her convalescence was uneventful.

Ten months later, August, 1944, she complained of pelvic pain and increasing dysmenorrhea. A pelvic examination revealed that the uterus was normal in size but retrodisplaced third degree and fixed. There was a cystic, tender mass 8 cm. in diameter in the left side of the pelvis and there was tenderness in both sides of the pelvis. Operation in

September, 1944, revealed a retrodisplaced uterus which was bound down by adhesions. The left ovary contained a chocolate cyst the size of a large lemon, and it was bound down in the posterior cul-de-sac by dense adhesions. It was necessary to remove the entire ovary. The right ovary was adherent to the posterior surface of the right broad ligament, and about one-half of this ovary was resected because of endometriosis. There were several dark, bluish, shot-like areas of endometriosis on the anterior surface of the uterus. The Fallopian tubes were congested and bound down; they were freed but not removed and the uterus was suspended.

This patient's convalescence was uneventful. After operation the menses were regular and she had very little dysmenorrhea. She was examined in May, 1948, and at that time the uterus was in an anterior position, soft, and symmetrically enlarged to the size of a six weeks' pregnancy. Her prenatal course was uneventful until the thirty-sixth week when she went into labor and was delivered spontaneously after an easy labor of thirteen hours. The baby was born alive and normal and weighed 2,806 grams.

Two months after delivery the uterus was in an anterior position and normal in size.

CASE 7.—A 29-year-old white woman was first examined in 1940. The chief complaints were dysmenorrhea and backache. She had been married for one year and had never been pregnant. Menses were regular every twenty-eight days, duration six to seven days, with severe pain the first three days. The history was nonrevealing. A pelvic examination revealed a normal cervix. The uterus was small, firm, retrodisplaced second degree and a little to the right of the midline. The uterus was replaced in an anterior position and a Smith pessary was inserted into the vagina. It was removed after a few days and the uterus remained anterior. The patient's condition remained satisfactory until 1946 when she had severe pelvic pain and a cystic mass 10 cm. in diameter was found in the left side of the pelvis.

Operation revealed a chocolate cyst 10 cm. in diameter which had destroyed the left ovary. The adhesions were separated and the left ovary, Fallopian tube and the appendix were removed. Her convalescence was uneventful and symptoms were relieved.

Five months after operation she was pregnant and had an early abortion. Her condition has remained good.

CASE 8.—A 29-year-old white woman was first examined in August, 1943. She had been married for one year and her only pregnancy had terminated in an early abortion. Menses were regular every twenty-five days, duration five days. She complained of increasing dysmenorrhea during the past eight months. Physical examination was essentially negative except for a tender, cystic mass the size of an orange which seemed to be an enlarged ovary bound down by adhesions in the posterior cul-de-sac and left side of the pelvis.

Operation was performed three weeks later. The left ovary was enlarged to the size of an orange, densely adherent in the posterior cul-de-sac and to the posterior surface of the left broad ligament. It was accidentally ruptured and a considerable quantity of dark, thick, chocolate-colored fluid was evacuated along with the shell of the left ovary. There were a few small, dark, bluish, endometrial implants in the left broad ligament and on the anterior surface of the bladder. The uterus was anterior, and the right ovary and both Fallopian tubes appeared to be normal. A diagnosis was made of endometriosis and a chocolate cyst of the left ovary.

Following operation the menses were normal until Jan. 21, 1944, four months after the operation. She then had an uneventful pregnancy and was delivered, at term, in November. Labor was slow and irregular and she was delivered with midforceps. The baby was alive and in good condition and weighed 3,600 grams. The mother's convalescence was uneventful.

CASE 9.—A 21-year-old white woman was first examined in November, 1943. She had been married for one year and had never been pregnant. The chief complaints were

pelvic pain and dysmenorrhea. Menses were regular every thirty-five days, duration five days. Physical examination was negative, except that the uterus was retrodisplaced third degree, small, firm, and fixed.

Operation was performed in September, 1944. The fundus of the uterus was retro-displaced third degree and bound down by dense adhesions. The left ovary was adherent in the posterior cul-de-sac and to the posterior surface of the left broad ligament. The adhesions to the left ovary and uterus were separated and the uterus suspended in an anterior position. Several small endometrial implants were found in both ovaries and on the posterior surface of the uterus. Her convalescence was uneventful, but the menses were every thirty to ninety days. Her husband returned from overseas in 1945 and pregnancy occurred soon after. Her condition remained good. She was delivered, with low forceps, at term in March, 1946, after a labor of sixteen hours. The baby was alive and normal and weighed 3,770 grams.

When last examined in March, 1949, the fundus of the uterus was in an anterior position and normal in size. The pelvis was otherwise normal. Menses occurred every thirty days with slight dysmenorrhea.

CASE 10.—A 24-year-old white woman was first examined in March, 1944. She had been married for one year. Menses were regular every twenty-eight days, duration four to five days. She complained of severe dysmenorrhea. Pelvic examination revealed a normal cervix. The uterus was retrodisplaced third degree, normal size and fixed. The right ovary was cystic, about 6 to 7 cm. in diameter and fixed in the posterior cul-de-sac. She was operated upon two weeks later. The uterus was found retrodisplaced third degree and bound down by adhesions along with both ovaries. Approximately one-half of each ovary was resected because of endometrial cysts. The adhesions to the uterus were separated and the uterus was suspended. The Fallopian tubes were not involved. The operation was followed by an uneventful convalescence.

She remained comfortable and menstruated regularly for six months. Following a menstrual period in October, 1944, she had an uneventful prenatal course and was delivered, with low forceps, at term after a labor of eighteen hours. The baby was alive and normal and weighed 3,373 grams. The mother's convalescence was uneventful. She had remained in good health. Menses are regular every twenty-eight days, duration five days with very little discomfort. The left ovary is a little larger than normal but the uterus is in an anterior position, freely movable, and normal in size and consistency.

CASE 11.—A 36-year-old white woman was first examined in January, 1945. She was pregnant without any complaints. She had been married four years and used a contraceptive only during the first year. Her last menstrual period occurred in June, 1944. Before the onset of pregnancy, menses had been regular every twenty-seven days, duration three to six days, with occasional dysmenorrhea the first day.

An examination revealed that the uterus was in an anterior position, soft, and symmetrically enlarged to the size of a six months' pregnancy. No abnormal pelvic masses were palpated. The diagonal conjugate was 10 cm. The pregnancy was uneventful until the onset of labor at term. Because of a flat pelvis and face presentation she was delivered by low cervical flap cesarean section of a living, normal child which weighed 3,175 grams.

At the time of operation numerous small, bluish areas of endometrial implants were observed on the anterior surface of the uterus and in both broad ligaments, but the ovaries appeared to be normal and there were no pelvic adhesions. Her convalescence was uneventful, and she has remained symptom free.

CASE 12.—A 33-year-old white woman was first examined in July, 1946. She had been married for eleven years but had never been pregnant. She complained of constant pressure in the pelvis but stated that her menses were regular every twenty-eight days with no increase in pain. A pelvic examination revealed that the cervix was normal. The uterus was retrodisplaced second degree and normal in size. There was a soft, cystic mass 8 cm. in diameter fixed in the left side of the pelvis and the posterior cul-de-sac.

She was operated upon the next day. At operation the uterus was found retrodisplaced second degree but otherwise it was normal. The left ovary was cystic and enlarged to 8 cm. in diameter. It was adherent in the left side of the pelvis and filled with a dark, chocolate-like material. This ovary was removed. There were numerous endometrial implants in both broad ligaments and along the posterior surface of the uterus. The adhesions around the right tube and ovary were freed.

Her postoperative course was uneventful and menses were regular until Aug. 18, 1947, following which she had an uneventful pregnancy and on May 29, 1948, she was delivered, vaginally, after a labor of five hours. The baby was alive and normal and weighed 3,645 grams. The mother's convalescence was normal.

Six weeks after delivery she was examined and the uterus was in an anterior position and normal in size. She had no complaints.

CASE 13.—A 23-year-old white woman was admitted to the Medical College Hospital on Nov. 8, 1944, with a chief complaint of pelvic pain for six hours. Menses had commenced at the age of thirteen years and usually occurred regularly every twenty-six to twenty-eight days with a duration of six days, with no dysmenorrhea until her marriage six months previously. She had never been pregnant, and after observation for two days she left the hospital.

One week later she was readmitted because of pelvic pain. Examination revealed a small, tender, cystic mass in the right side of the pelvis in close proximity to the uterus. She was operated upon on Nov. 18, 1944. A cystic mass the size of a small orange was found involving the right ovary and firmly adherent to the rectouterine fossa. In an attempt to remove the cyst, it was ruptured and a considerable quantity of chocolate-colored fluid was spilled. Most of the right ovary was removed and also the appendix. The Fallopian tubes and the left ovary appeared to be normal. The diagnosis was endometriosis of the right ovary.

She was first examined in our office in October, 1946. Following the operation, menses had been regular and normal and her last menstrual period occurred on July 12, 1946. Physical examination revealed no unusual findings. The fundus of the uterus was in an anterior position, soft, and symmetrically enlarged to the size of a three months' pregnancy. Her prenatal period was normal and she was delivered, with low forceps, on April 18, 1947, after an uneventful labor of eleven hours. The baby was alive and normal and weighed 3,316 grams.

A second pregnancy in 1948 was uneventful and the patient was delivered at term. The duration of labor was seven hours and the baby was alive and normal.

Comment

Thirteen cases have been reported, in twelve of which pregnancy occurred after a conservative operation for endometriosis (Tables I and II). The thirteenth patient had endometriosis during pregnancy but it was undiagnosed until she was delivered by cesarean section.

TABLE II. RESULTS OF PREGNANCIES IN THIRTEEN PATIENTS WITH ENDOMETRIOSIS

Term pregnancies	14
Abortions	2
Total pregnancies	16

This table shows that sixteen pregnancies occurred in thirteen patients with endometriosis. In twelve patients pregnancy followed a conservative operation for endometriosis. In one patient endometriosis was not diagnosed until she was delivered by cesarean section. Fourteen of the pregnancies resulted in term or near-term deliveries of normal living babies.

The presence in the private practice of one physician of this number of patients in whom pregnancy occurred after endometriosis indicates that the

condition is more frequent than is usually reported. It further indicates that conservative surgery for endometriosis in women in the child-bearing period, particularly in young women and those without children, is justifiable. In young women with endometriosis which is not too extensive, the child-bearing function can be preserved by a conservative operation and pregnancy frequently follows this treatment. Even after partial resection of both ovaries because of endometriosis, normal pregnancy occurred in three of our patients.

In four of the patients seven pregnancies had occurred before the endometriosis was recognized. This causes one to question whether pregnancy early in the reproductive period has an inhibitory effect on endometriosis.

Endometriosis is a well-recognized cause of infertility. Several of our patients had been sterile for years, although married and living a normal sexual life. After removal of a chocolate cyst, separation of adhesions, and sometimes a suspension of the uterus, pregnancy occurred quickly. It seems probable that the pelvic pain and discomfort associated with endometriosis are increased at times by intercourse. This may decrease the frequency of intercourse and consequently it reduces the possibility of conception.

We are unable to explain the apparent arrest of endometriosis in some patients after an operation in which one ovary or a part of both ovaries was left without removal of all of the implants and involved tissue. Several of these same patients have had pregnancies and remained comfortable for years after the operation.

One patient (Case 11) gave no symptoms suggesting endometriosis and the disease was recognized at the time of cesarean section by the presence of several small endometrial implants on the posterior surface of the uterus and in both broad ligaments. It seems reasonable to think the endometriosis was present before pregnancy occurred.

The indications for surgery in the twelve patients operated upon because of endometriosis were usually increasing dysmenorrhea, pelvic pain associated with a tender, cystic mass in either one or both sides of the pelvis, and sometimes a retrodisplaced uterus, which seemed to be fixed. The indications for operation were definite in all of the patients.

TABLE III. INCIDENCE OF PREGNANCY AFTER OPERATION FOR ENDOMETRIOSIS
ACCORDING TO AGE AT TIME OF OPERATION

CASE NO.	AGE IN YEARS			
	21-25	26-30	31-35	36-40
1		1		
2				1
3			1	
4		1		
5		1		
6			1	
7				1
8		1		
9	1			
10	1			
12			1	
13	1			
No. patients	3	4	3	2
No. term pregnancies	4	6	3	
No. abortions				2

This table shows that successful pregnancy after operation for endometriosis occurred most frequently in patients operated upon before they were 36 years old. In two cases in which abortion followed operation the patients were aged 37 (Case 2) and 36 years (Case 7). Case 11 was omitted in this table because the operation was performed during pregnancy.

An analysis of our twelve patients (Table III) in whom pregnancy occurred after operation shows that three were between 22 and 25 years of age at the time of operation, and they later had four babies. Four patients were between 26 and 30 years of age at the time of operation and they later had six babies. Three patients were between 31 and 35 years of age and following the operation they had three babies. In both of the patients between 36 and 40 years of age, pregnancy occurred after conservative operation for endometriosis, but these two patients had early abortions. Thus, though the number of cases reported by us is small, it seems to indicate that the prognosis for a successful pregnancy is better in young women with endometriosis than it is for those over 35 years of age.

Three patients conceived after separation of adhesions and partial resection of both ovaries. Six patients in whom the uterus was suspended at the time of operation for endometriosis later conceived, and seven normal babies were delivered in this group. In two patients, conception occurred after the left tube and ovary were removed. In three patients an ovary was removed but both Fallopian tubes were left, and all three of these patients later became pregnant.

In both patients in whom an abortion occurred the uterus at the time of operation was in an anterior position.

All thirteen of the patients have remained well except Case 7, operated upon in 1946, and Case 8, operated upon in 1943. Both of these have had increasing slight pelvic pain during the past four months, and it may be necessary to resort to surgery again for them.

Summary

The literature has been briefly reviewed to show the prevalence of endometriosis in women of child-bearing age.

The concurrence of endometriosis and pregnancy in our cases, as well as in the literature, has been emphasized.

Thirteen cases have been presented in which pregnancy occurred in women with endometriosis. In twelve of these, pregnancy occurred after conservative surgical procedures. In the remaining case, endometriosis, without symptoms, was observed at the time of cesarean section.

Conservative surgical treatment, with preservation of the child-bearing function in young women and those without children, is recommended whenever possible in cases of endometriosis.

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Discussion

DR. JEAN P. PRATT, Detroit, Mich.—We are indeed grateful to Dr. Ware for bringing to our attention the fact that pregnancy and endometriosis could be associated without one interfering with the other. He also has emphasized the importance of conservatism in the treatment of endometriosis, which is very important. I quite agree that there are many more cases of pregnancy and endometriosis than have been reported and it is a great deal more common probably than we know. That was illustrated by the one patient in whom he found endometriosis at the time of cesarean section with no reason to suspect its presence before nor did it have an influence on the course of the pregnancy.

It is interesting to review briefly the over-all picture of the development and concept of endometriosis. It is 100 years since the first case was described but not named. The condition was found at necropsy. In the next ten to twenty years cases appeared in the literature; these were only the most advanced cases. It was in 1890 when von Recklinghausen was present at an operation that he carefully described endometriosis and it was thus established as an entity. In the early days the ending "itis" was given; later work by Cullen gave it the "oma" ending indicative of tumor formation. The term now accepted is endometriosis and represents a condition and not inflammation or tumor. The condition is not necessarily progressive. Apparently something happens some time in the patient's life and endometriosis becomes implanted. It may be innocuous and never progress farther than implantation.

Reports in the literature are based too much on the findings of this condition at operation. We have seen a large number of women for routine pelvic examination and we have trained ourselves to check for endometriosis in the pelvis as a very small lesion. We have been able to follow a large number of patients with endometriosis and we find it is not necessary to advise any treatment whatsoever for many of them because the condition remains stationary and there is no reason for treatment.

In patients with endometriosis, dysmenorrhea is a common symptom and is present in about 50 per cent of cases. When dysmenorrhea and endometriosis are present in the same patient, it has been assumed that the endometriosis was the cause of dysmenorrhea. When it was suggested that testosterone would diminish the activity of endometriosis, a good means of testing whether dysmenorrhea is due to endometriosis was offered, because, when testosterone is given, the symptoms should subside if they are due to endometriosis. When we have suspected endometriosis with dysmenorrhea it has been our practice to try testosterone and if we get relief we are satisfied that we are dealing with an organic condition. If the patient is not relieved we believe the dysmenorrhea is due to some psycho-

somatic origin. By careful selection of this group it becomes possible to sort out certain patients and treat them as psychosomatic rather than assume that endometriosis is the underlying trouble. Bearing that in mind will save a lot of needless operations.

In regard to pregnancy and endometriosis I have in mind two patients who illustrate our practice when these conditions occur at the same time. If we find a small lesion we usually advise the patient to have her pregnancies without delay because in these patients infertility develops into sterility so that it is well to have the pregnancies as early as possible. If, after a period of two or three years, no pregnancy ensues, we may advise those patients that an operation might give them an opportunity for pregnancy. One such patient had three pregnancies after she had had one ovary and half of the other resected to relieve the symptoms of an extensive endometriosis. That surgical procedure had no effect on her pregnancy or labors.

Another patient illustrates a second point. She had dysmenorrhea. She also had infertility and was obsessed with the idea of becoming pregnant. In a test for infertility a tubal insufflation was done and no air went through the tubes. We did not tell the patient she was sterile and it was not long before she became pregnant and has had three babies since then. But we could not demonstrate that the tubes were open.

So we have a number of patients with known endometriosis who do go through normal pregnancies. In such patients there is usually very little change except softening of the endometriosis but in general it is our experience that the lesion does not increase.

On the whole, I think the majority of patients develop endometriosis as a single incident and the condition becomes more or less static. We know from the stories of others that there is extension of the process to surrounding tissue and that they do have continued and increased trouble, but that is not the rule. If you look for early endometriosis you can follow many of these patients and allow them to proceed with a normal life.

DR. WALTER DANNREUTHER, New York, N. Y.—Dr. Ware's paper demonstrates that while endometriosis is a factor in sterility, pregnancy may occur after surgical treatment of existing lesions as well as in the presence of endometriosis. All pelvic surgeons of long experience must have been impressed by the apparent recent increase in this disease. Certainly I have seen proportionately many more cases during the last twenty years than in the previous twenty. If Sampson's theory of retrograde spill accounts for the greater part of the incidence of pelvic endometriosis, it would seem logical to attribute some of it to the pernicious practice of plugging the vagina and obstructing menstrual drainage, thereby forcing endometrial detritus out through the fimbriated extremities of the tubes.

One often operates upon patients with a large chocolate cyst in one ovary in which the pathologist cannot identify endometrial glands because the cellular elements have been destroyed by pressure necrobiosis and leakage. I have personally operated upon about 500 women who had ample gross pathologic evidence of endometriosis, but in only about two-thirds of them could the pathologist make a diagnosis on the tissue submitted. The latter group has included some thirty instances of women of 25 years or younger, and two were less than 21.

Surgical judgment is important regardless of age, and I would go farther than Dr. Ware who states that conservative surgical treatment is "often justifiable," and insist that it is always indicated. Even in cases of apparent extensive ovarian destruction, careful search should be made for areas of normal ovarian structure, no matter how small. While it is true that a certain percentage will require re-operation later, menstruation can nearly always be preserved. Remote implants in the colon and rectovaginal septum will often regress without complete castration, and one is occasionally rewarded by a subsequent pregnancy.

DR. JOE V. MEIGS, Boston, Mass.—I think the number of pregnancies following Dr. Ware's surgery is very impressive. In the literature between 9 and 29 per cent of pregnancies occurred following conservative treatment. In our two series 12 and 28 per cent followed conservative surgery.

A few years ago I read a paper before the Southern Surgical Association. Dr. Arthur W. Allen of Boston said to me: ''Do say something about conservatism in the surgery of endometriosis.'' He felt that many surgeons were operating on these patients and removing their ovaries because Sampson had said it would cure the disease. I believe that castration is rarely necessary and that endometriomas can safely and easily be removed from the ovaries. This certainly applies to the young and, I think, to those near the menopause as well. My plea is for conservatism in the treatment of endometriosis.

DR. JOHN ROCK, Brookline, Mass.—I think the diagnosis of endometriosis would be a little broad in those cases where we find a few blue spots on the bladder peritoneum or in the posterior cul-de-sac. Of course, we would be conservative with those; but I would add my word to that of Ware and Pratt and Dannreuther that even in the case of massive endometriosis, conservatism is still in order. I remember one patient whose pelvis contained bilateral and enormous chocolate cysts that completely filled the left side of the pelvis and so much of the right side that I could find only a small bit of the right ovary. That patient has been twice delivered normally after conservative surgery was done.

DR. KARL MARTZLOFF, Portland, Ore.—I would like to ask Dr. Ware if he can tell us who was the first investigator to recognize the response of this ectopic endometrium to ovarian stimulation. Credit has been given to Sampson but I believe that is incorrect.

I would also like to ask Dr. Ware whether the ectopic endometrium in these patients who become pregnant showed any consistent type of histologic pattern. I have in mind the fact that in many of these cases the endometrium is often of the so-called basal type and apparently is not responsive to ovarian stimulation, whereas in other patients the ectopic endometrium shows unmistakable secretory changes, is therefore definitely responsive to ovarian stimulation, and is a source of bleeding.

DR. WARE (Closing).—I am sorry that I cannot give Dr. Martzloff a positive answer to his question. As stated in my paper, Cullen in 1895 reported a case of adenomyoma of the uterus, and Russell in 1896 described the occurrence of adherent endometrium in the ovary. The term ''endometriosis'' seems to have been popularized by Sampson whose paper on ''Perforating Hemorrhagic (Chocolate) Cysts of the Ovary'' was published in 1921. The same author published numerous papers on ''Endometriosis'' during the next few years.

PREGNANCY AND DIABETES*

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(From the Department of Obstetrics and Gynecology and the Department of Medicine of the New York Hospital and Cornell Medical College)

PREGNANCY in a diabetic is no longer a rarity. Since insulin has prolonged the life of the young diabetic, more physicians have been called upon to advise and care for the diabetic expectant mother. It is the purpose of this communication to present our experience in treating 106 diabetics in 131 pregnancies. This study is presented because of the paucity of detailed reports currently available and because our management has differed from that employed by some others in that we have not employed hormonal therapy or strict chemical control of the diabetes.

Material

Our material consists of all cases seen in a large teaching-obstetrical service associated with a general hospital. The 106 cases included 35 primigravid and 71 multigravid patients. There were 21 patients who had more than one pregnancy at our hospital after the diabetes became established. All cases of questionable diabetes have been excluded.

1. *Race and Age.*—Twenty-four patients were Negroes. This is two and one-half times the clinic incidence. The average age was 30.2 years. There were 5 patients under 20 years of age; 58 patients between 21 and 30; 60 patients between 31 and 40; and 8 patients over 41 years of age at the time they registered for pregnancy (Fig. 1).

2. *Past History.*—The 71 multigravid patients gave a history of 243 previous pregnancies in other hospitals. There was no significant history of infertility or high incidence of abortion. Sixty-two per cent of these pregnancies terminated with living infants. Of the remainder, 13 per cent terminated with spontaneous abortion, 7 per cent with induced abortion, and 18 per cent with the delivery of deadborn or living infants that died during the neonatal period. Historical data reveal an infant mortality of 18 per cent.

The weights of these infants indicated that many were of excessive size. If we consider the infant weights of previous pregnancies of the patients in whom the diabetes was discovered in this pregnancy, we find that 52 per cent weighed 8 pounds or over (3,636 grams) (Fig. 2). The average weight of fullterm white infants in our clinic is 3,224.6 grams or 7.1 pounds, and slightly less for Negro infants. Miller, Hurwitz and Kuder,[11] reporting on the past histories of diabetic patients whose infants were delivered and weighed on their respective services, found that the infants were generally larger than average in both the diabetic mother and in those mothers who later developed diabetes.
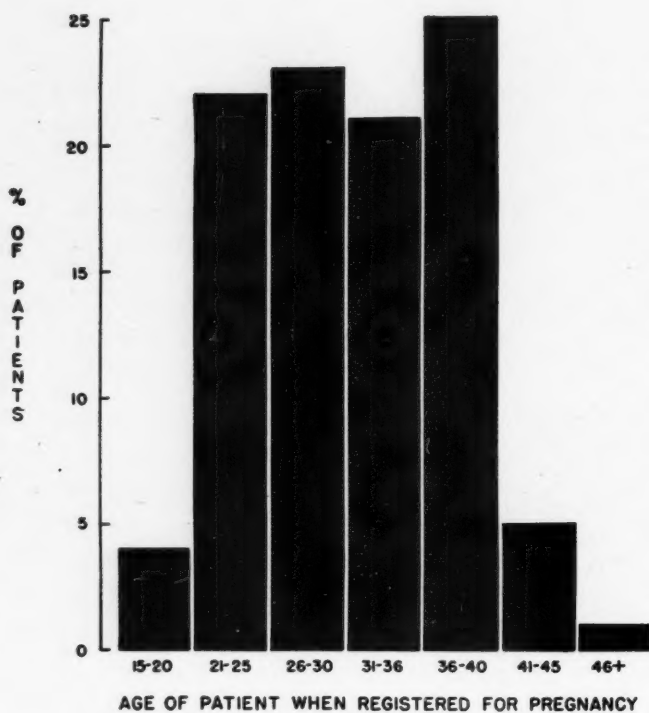
AGE DISTRIBUTION

Fig. 1.

WEIGHT DISTRIBUTION OF INFANTS FROM PREVIOUS
PREGNANCIES OF PARENTS IN WHOM DIABETES WAS
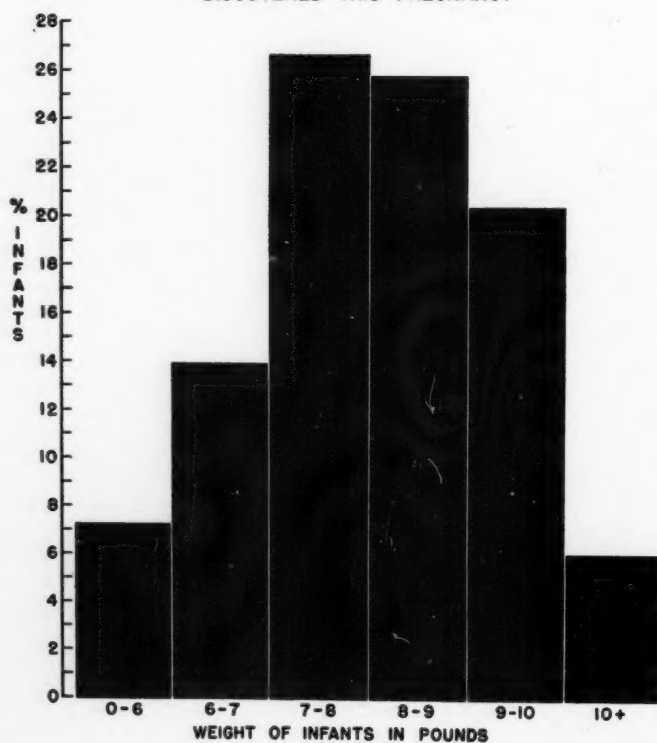DISCOVERED THIS PREGNANCY

Fig. 2.

Pregnancy

The diabetic patient was followed in both the antepartum and diabetic clinics, and thus seen frequently and at alternate visits by both obstetrician and internist. Close supervision by both was maintained after admission to the hospital.

1. *Duration.*—Ninety-eight of the 131 pregnancies (75 per cent) terminated after the thirty-sixth week. Of the remaining 33 pregnancies, there were 10 spontaneous and 4 therapeutic abortions, 1 ectopic pregnancy, and delivery of 4 premature and 11 mature infants (Fig. 3).
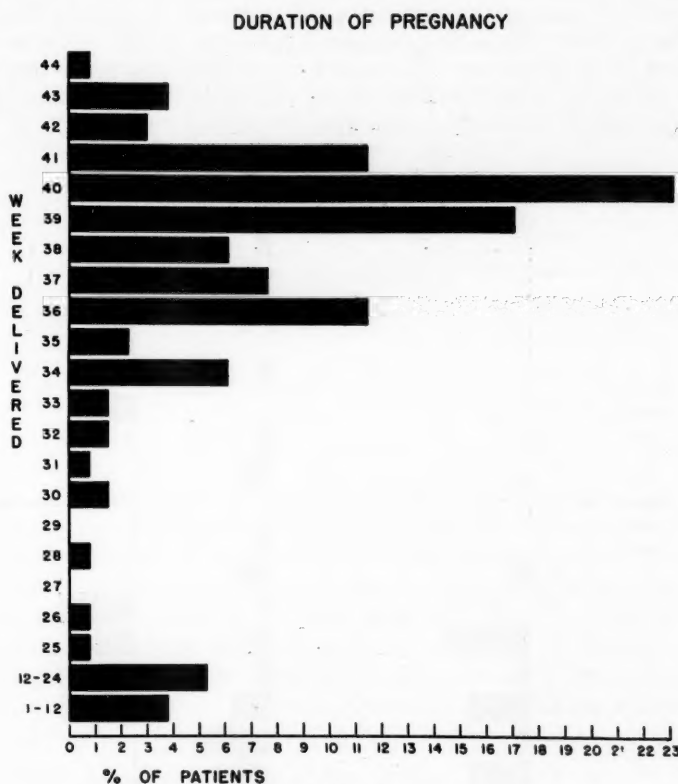
DURATION OF PREGNANCY

Fig. 3.

2. *Weight Gain.*—Stander and Pastore[19] found the average weight increase from the sixth to the fortieth week of pregnancy in the nondiabetic patient to be 13.6 kilograms (an average of 400 grams a week). The average patient, they found, gains 24 per cent of her original weight. In our series of diabetic patients, not all of the patients knew their nonpregnant weight precisely; 70 per cent of the patients were overweight when first seen. Thirty per cent of the patients who registered in the first trimester gained over 400 grams a week; 31 per cent of those who registered in the second trimester and 66 per cent of those who registered in the third trimester gained over the theoretical average of 400 grams. This would imply that with the exception of the third trimester group, weight gain was not excessive and well under control. The fact that 66 per cent of the group that registered in the third trimester gained over 400 grams a week is partially explained by the knowledge that the physiological weight gain per week is higher in the last trimester,

and by the fact that the incidence of toxemia was higher in this group. Weights of 12 per cent of the patients remained stationary or decreased as a result of dieting (Fig. 4).

3. *Complications of Pregnancy Other Than Diabetes.*—The incidence of toxemia,* excluding vomiting of pregnancy, in our series was 46 per cent (60 patients) (Table I). Specifically, 25 patients had symptoms of mild pre-eclampsia, 11 of severe pre-eclampsia, and one patient had convulsions typical of eclampsia. Hypertensive disease was diagnosed in 21 patients, which represents a higher incidence than was found among the clinic population and represents a higher proportionate incidence among the patients with toxemia. It is to be noted that in this series of diabetic patients, toxemia was three times as prevalent among the multigravid patients as among the primigravid patients. The general clinic incidence of toxemia of all types is 6.3 per cent, which means that toxemia was seven and one-half times more prevalent among our diabetic patients and the high fetal mortality rate reported may be attributed in significant measure to this fact.

AVERAGE WEIGHT GAIN PER WEEK
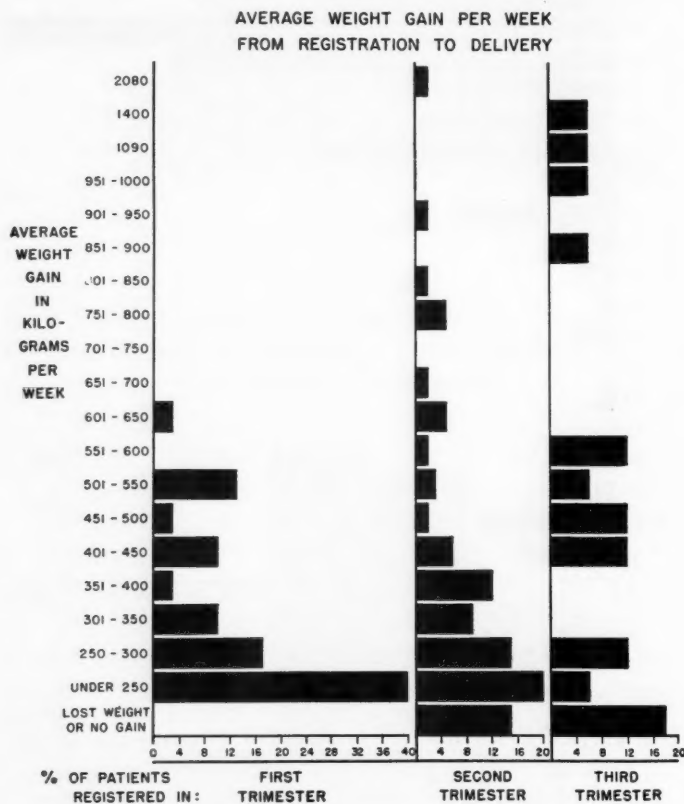FROM REGISTRATION TO DELIVERY

Fig. 4.

Of the other complications of pregnancy, urinary tract infection and pneumonia had a significant incidence in our series. It is to be noted that there were only two definite cases of hydramnios.[12] This low incidence does not correspond to the experience of White and others who report a higher incidence.

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*By definition of the American Committee on Maternal Health, 1927, toxemia includes hypertensive disease, renal disease, pre-eclampsia, mild and severe, eclampsia, vomiting of pregnancy, and unclassified types.

TABLE I. COMPLICATIONS OTHER THAN DIABETES

DISEASE	NO. PRIMIPARAS	NO. MULTIPARAS	TOTAL NUMBER
Hypertensive disease	2	19	21
Mild pre-eclampsia	6	19	25
Severe pre-eclampsia	5	6	11
Eclampsia	1		1
Nephritis	1	1	2
Cystitis			5
Pyelitis and pyelonephritis			5
Pneumonia			4
Syphilis			5
Others			16

The Diabetes

1. *Duration.*—The duration of the diabetes varied from one to twenty-two years, and the details are shown in Table II. Fifty-nine of our patients knew of their diabetes prior to gravidity and 47 patients learned of their diabetes during pregnancy or post partum. The age of onset of diabetes is summarized in Fig. 5. Twenty-three per cent of the patients can be considered juvenile diabetics.

TABLE II. DURATION OF DIABETES BEFORE THIS PREGNANCY

NUMBER OF YEARS	NUMBER OF PATIENTS
1-3	18
4-6	17
7-9	14
10-12	5
Over 12	5

2. *Treatment.*—Prior to the discovery of protamine insulin, that is, 1936, the few patients we observed were treated by the chemical technique which aims at the maintenance of a sugar-free urine and a normal blood sugar.

After 1936, our criteria for satisfactory control were changed. From our experimental and clinical observations with this hormone we were led to the adoption of clinical rather than chemical standards of control. Briefly, our data established that when protamine insulin, or a mixture of protamine and regular insulin were used, it was *not essential to aim at a sugar-free urine or bring the blood sugar to normal levels as long as the patient:*

    a. Was maintaining or gaining weight.

    b. Had none of the symptoms of diabetes (thirst, frequency, polyuria, hunger, fatigue, pruritus, or visual disturbance).

    c. Had no ketonuria.

We have used these clinical guides during the past twelve years and during this period there appeared to be no need for routine hospital admission because of the diabetes per se. A persistent glycosuria in the absence of the above criteria was no indication for hospitalization. We advised a self-selected, unmeasured diet excluive of sweets, vitamins and enough protamine insulin, or a mixture of protamine and regular if necessary, to maintain our patient controlled by our criteria. The precise details of the treatment can be found in our previous publications.[21] Rigid diets were imposed when obesity was also a consideration.

Using this clinical approach we did not observe a consistent diminution of the insulin needs during pregnancy as some observers have described. In some patients the unitage was raised and in others lowered. Fifty-three required

no insulin.   Of the remaining 78 pregnant patients who needed insulin, 13 re-
quired more, 11 needed less, and no change of the insulin dosage was observed in
the remaining 54 pregnancies.   It was noted that 41 (70 per cent) patients
required less insulin after delivery.   The minimum insulin dosage was 10 and the
maximum 120 units daily.   Half of the patients required from 40 to 60 units
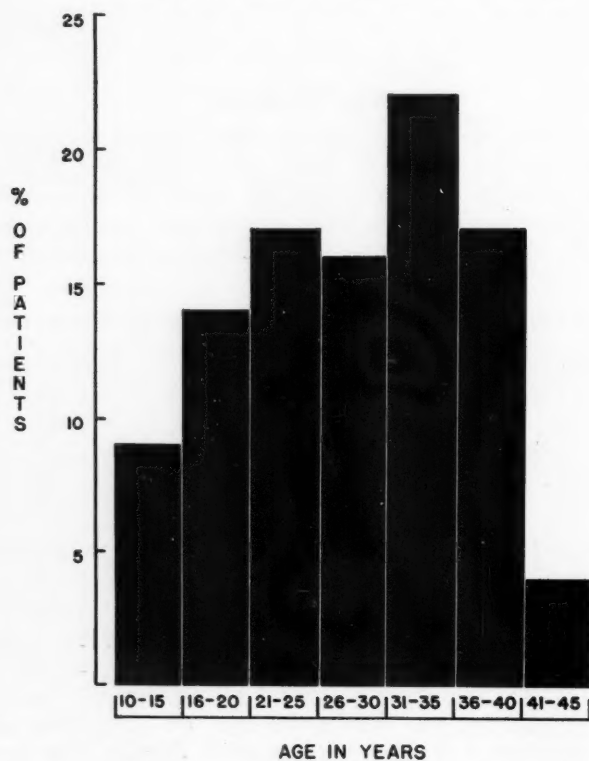of insulin per day (Figs. 6 and 7).

AGE OF PATIENTS AT ONSET OF DIABETES

Fig. 5.

Labor

In 25 per cent of our series labor ensued before the thirty-sixth week.
The duration of labor of the entire series was under 10 hours in 44 per cent
of our primigravid and 70 per cent of our multigravid patients.   By our clinic
standards labor is considered prolonged when it is over 30 hours, and, using
this arbitrary criterion, labor was prolonged in 26 per cent of our primigravid
and in only 1.3 per cent of the multigravid patients.   Our findings definitely
indicate that the duration of labor is appreciably lengthened in the primi-
gravid diabetic patient as compared with the nondiabetic.   In the latter the
clinic incidence of prolonged labor, by our criteria, for all patients was 9 per
cent, varying slightly from year to year (Fig. 8).

1. *Type of Delivery.*—In 13 patients, vaginal deliveries were accomplished
by forceps.   This is an incidence of only 10 per cent, whereas the incidence of
forceps operation of the clinic is closer to 20 per cent.   There were two de-
structive operations on dead infants of excessive size.   The incidence of breech
presentation was 9.9 per cent, three times the clinic average (Table III).

TABLE III. TYPE OF DELIVERY, 131 PREGNANCIES

	NUMBER	PER CENT
Abortions.—	14	
Spontaneous	10	7.6
Therapeutic	4	3.5
Spontaneous delivery	97	74.2
(including abortions)		
Operative delivery.—	34	26.8
Low forceps	9	
Midforceps	2	
High forceps	2	
Breech extraction	6	
Craniotomy	2	
Cesarean section	13	9.9
Manual removal of placenta	2	
Incidence of breech presentation		9.9

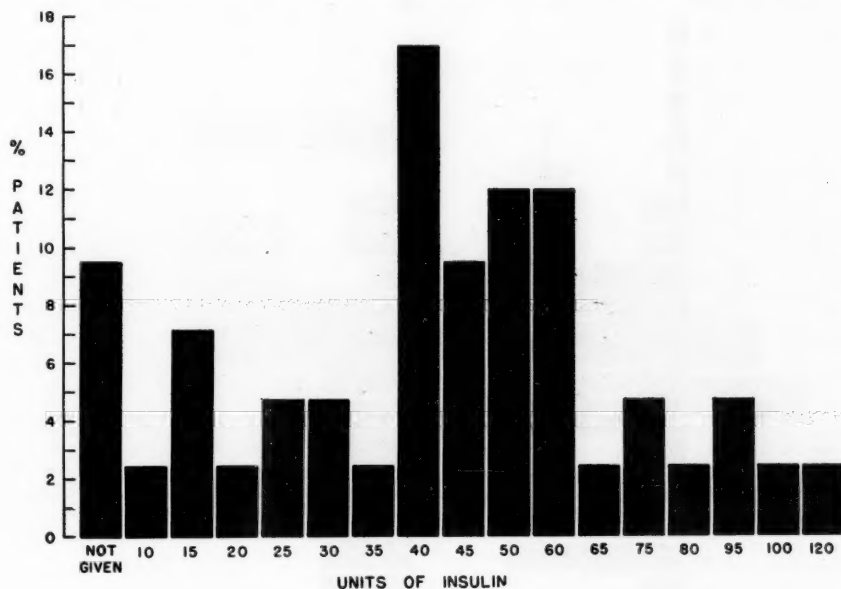TOTAL INSULIN DOSAGE OF 42 PATIENTS PRIOR TO PREGNANCY

Fig. 6.

2. *Cesarean Section.*—This was done in 13 patients, an incidence of 10 per cent, which is three times the clinic average. Severe pre-eclampsia was the most frequent and serious indication, accounting for six cases. The other indications for cesarean section are tabulated on Table IV. In general, the indication for cesarean section was of an obstetrical or complicating medical nature and not the diabetes per se. One patient whose diabetes was severe and in whom a large infant was demonstrated was the only exception.

3. *Complications of Labor and Delivery.*—As a rule the deliveries were not unduly difficult, as shown by the little need for forceps (10 per cent). However, considerable difficulty was encountered with the delivery of the shoulders in a number of the larger infants. There were 8 instances of shoulder dystocia with 4 deaths resulting from traumatic delivery. These cases are described below in detail.

Postpartum hemorrhage (blood loss of 500 c.c.) was noted in 4 cases, an incidence of 3 per cent and twice the clinic average. Premature rupture of

the membranes occurred in 14 cases (exclusive of abortions). There were two
instances of retained placenta and one case each of prolapse of the cord and
face presentation.

TABLE IV. INDICATION FOR CESAREAN SECTION (9.9%)

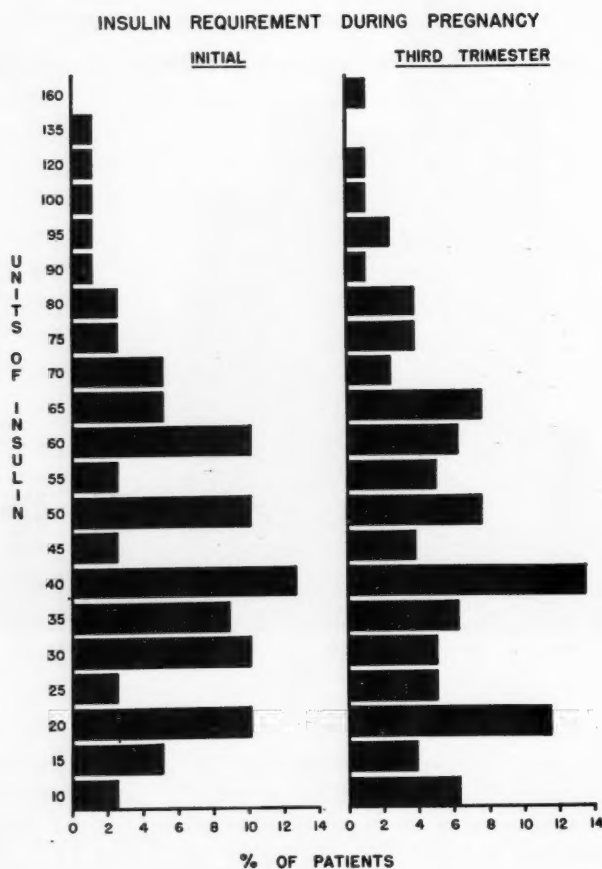|	
Severe pre-eclampsia	6
Hypertensive disease	1
Transverse presentation	1
Breech with lack of progress in severe diabetic	1
Severe diabetic with large infant	1
Previous section	1
Cephalopelvic disproportion	1
Posttraumatic psychoneurosis	1

Fig. 7.

Maternal Morbidity and Mortality

The incidence of postpartum morbidity was 17 per cent, with intrauterine
infection being the most frequent cause, and pyelitis playing a secondary role
(Table V). Two deaths were recorded for the entire series. Both occurred
in the early years of the service, before the advent of chemotherapy and the
establishment of a blood bank. The first was a 34-year-old, para iv, gravida
viii, in whom diabetes was discovered post partum. The pregnancy was com-
plicated by an acute hydramnios and a difficult midforceps delivery after

twenty-one hours of labor. She was delivered of a large dead infant and she died 10 days later of a generalized peritonitis and pyelonephritis. The second maternal death occurred in a 40-year-old, para ii, gravida iv, whose diabetes was of two years' standing. Her diabetes was mild and did not require insulin. Because she suffered from hypertension and the size of the infant was excessive, a cesarean section was done. She died from hemorrhage the first day postoperatively. It would appear that the diabetes had little influence on the unfortunate outcome in these cases.

TABLE V. MORBIDITY, 131 PREGNANCIES

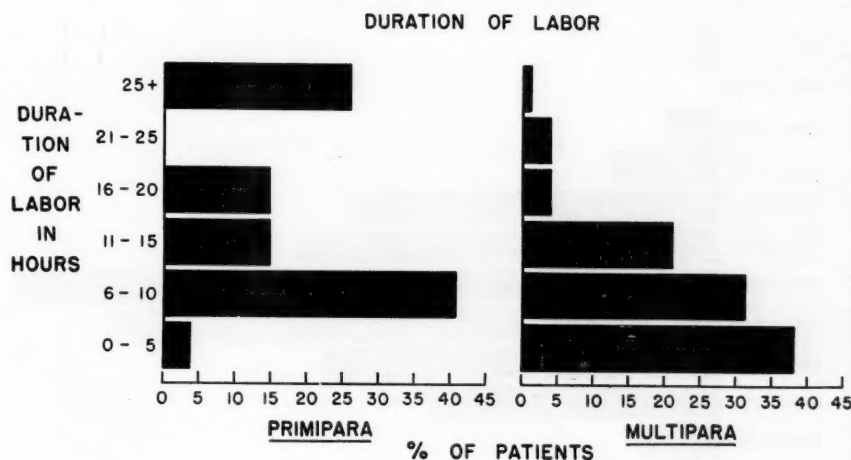| CAUSE	NUMBER OF PATIENTS
Puerperal	14
Mastitis	1
Pyelitis and cystitis	4
Wound infection	1
Septicemia	2
	22 = 17%

Fig. 8.

Care of the Infant*

Infants born to diabetic mothers are frequently of excessive size; their activity is poor and their respirations are sometimes established with difficulty. The babies may reveal a brawny generalized edema, cyanosis of the lips and extremities and dyspnea. The x-ray often shows generalized cardiac enlargement and though the blood count is normal one may find an abnormally high number of nucleated red blood cells in the smear.

These babies were transferred routinely to the pediatric service where, in selected cases, they were (1) placed in oxygen, (2) given glucose about six hours after birth and (3) after three feedings, the routine evaporated milk formula containing 70 calories per 100 c.c. At times gavage feedings were instituted because many of these infants were sluggish and poor feeders. Their fluid replacement was the same as for the normal, that is 100 c.c. per kilogram by the third day and 150 c.c. per kilogram by the seventh day.

*We are indebted to Dr. Thomas Moser and the Department of Pediatrics for their contribution to this study.

Complications which were encountered were: (1) Failure of the baby to maintain his normal temperature. If this condition persisted for more than twelve hours, the baby was placed in an incubator with constant heat and humidity provided. (2) Increasing cyanosis or twitching, which may have been due to an inadequate airway, too low an oxygen concentration, or to intracranial hemorrhage and secondary atelectasis. (3) Traumatic injuries secondary to difficult delivery. These were of many types including fractured skull, clavicle, or humerus, Erb's paralysis and facial paralysis. There was no significant incidence of associated congenital anomalies in our infants.

Recent investigators do not believe that parenteral glucose is necessary. Under control studies, babies who were given glucose intravenously did no better than those who were not. Normal newborn infants have been found to have a wide range of values of blood sugar ranging from zero to 100 mg. per cent. There is a similar range of values for infants of diabetic mothers. Only when such symptoms as convulsions and collapse accompany the hypoglycemia it is necessary to resort to parenteral administration of glucose with or without epinephrine.
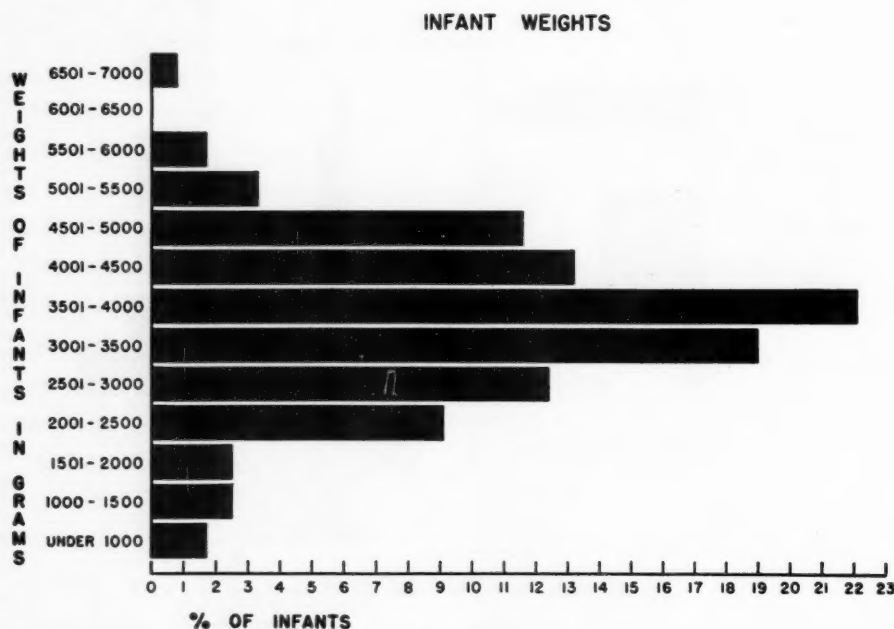

Fig. 9.

With the treatment as outlined, we were usually able to remove the baby from oxygen after a variable length of time, often under a week. The edema was lost in a few days resulting in an apparent excessive weight loss. The enlarged heart often returned to normal size within two months, or even a shorter period and there was rarely any residual heart disease. The inactivity and poor feeding resolved spontaneously within one or two weeks. Thereafter, the treatment of the infant was no different from that of the normal newborn.

Weight of the Infant

In Fig. 9 is summarized the weight distribution of all infants recorded. It is apparent that 30.6 per cent were over 4,000 grams, and that over 50 per cent weighed more than the average clinic weight of 3,250 grams.

Infant Mortality

There were 10 spontaneous abortions (7.6 per cent), 4 therapeutic abortions and 4 immature infant deaths. There were 6 premature and 22 mature infants* who died either in utero, during delivery, or in the neonatal period. Our fetal mortality, on the basis of these 28, is 21.4 per cent (Table VI).

TABLE VI. RESULTS, 131 PREGNANCIES

Spontaneous abortions	10 (7.6%)
Therapeutic abortions	4
Immature infant deaths	4
Premature infant deaths	6
Mature infant deaths	22
Fetal mortality (28 cases)	21.4%

Severity of the Diabetes and Infant Mortality

Has a mild diabetic prospective mother a better chance for a viable infant than one whose diabetes is moderately severe or severe? To attempt an answer to this question, data concerning the mothers of the 32 dead immature, premature and mature infants were re-evaluated, particularly concerning their diabetic status, with special reference to incidence of keto-acidosis, toxemia, traumatic delivery and other causes of infant death (Tables VII and VIII).

TABLE VII. ANALYSIS OF ALL INFANT DEATHS EXCLUDING ABORTIONS

	DIABETICS REQUIRING NO INSULIN	DIABETICS REQUIRING INSULIN
Number	12	20
Incidence of.—		
Juvenile diabetes	1	8
Toxemia	8	8
Keto-acidosis	0	8
Delivery.—		
Spontaneous	10	11
Operative	2	9
Infant Deaths.—		
In utero	7	9
During delivery	1	2
Post partum	4	9
Infant Weights.—		
Immature	2	2
Premature	2	4
Mature	8	14

Of the 32 patients whose infants died, excluding abortions, 12 were mild diabetics requiring no insulin, whereas the other 20 patients required insulin. In the entire series, 53 patients did not require insulin.

An analysis of the 12 patients requiring no insulin and whose infants died reveals that only one of this group could be classified as a juvenile diabetic (age of onset, 19 years). Five patients learned of their diabetes in their pregnancy for the first time, 5 prior to pregnancy, and 2 post partum. There was no history of previous insulin requirements and no history of acidosis or coma either before or during the pregnancy. Eight of these patients revealed evidence of a toxemia (66 per cent), with 5 showing mild preeclampsia and 3 hypertensive disease.

*We define abortion as the birth of a fetus weighing under 499 grams; immature infants 500 to 1,499 grams; premature infants, 1,500 to 2,499 grams, and mature infants over 2,500 grams.

Spontaneous delivery occurred in 10 of 12 cases, with one case of prolonged labor (84 hours).

The time of infant death, in this group of 12 mild diabetics requiring no insulin during their gravid period, was of interest.

1. *Died in Utero.*—Seven infants of the 12 patients requiring no insulin died in utero, and even though the diabetes was mild, 6 of the 7 patients *had evidence of toxemia*. A more detailed breakdown showed that 2 infants were immature, 1 was premature, and 3 were of excessive size. These findings lead to the conclusions that (a) toxemia develops frequently even in the mild diabetic who is pregnant, and (b) that one cannot exclude it as a factor contributing to the death of the infant.

2. *Died During Delivery.*—One infant weighing 5,190 grams died during delivery. The shoulders were very large and became impacted in the pelvis, necessitating excessive traction for delivery of the shoulders.

3. *Died Post Partum.*—Four infants died post partum. One of these was premature and one of excessive size. The latter infant had atresia of the pulmonary valve and succumbed from congenital heart disease with failure.

Of the 20 patients whose diabetes required insulin for clinical control, and who also lost their infants, 11 were aware of their diabetes *prior* to their pregnancy. Eight of these were juvenile diabetics. The insulin dosage prior to gravidity ranged from 15 to 110 units and there was no indication that the duration of the pregnancy had any effect on the insulin need. About one-third of the group needed less insulin; one-third needed more; and the remainder continued on the usual dosage.

Keto-acidosis occurred in 8 of this group of 20, requiring hospitalization for treatment. This will be discussed in detail below.

Delivery was spontaneous in 11 of the 20 cases. There were 2 cases of prolonged labor of 54 and 84 hours each, and 8 of the 20 patients (40 per cent) had toxemia.

1. *Died in Utero.*—Nine infants died in utero. Seven of the 9 cases were complicated by toxemia. One of the infants was premature and 2 were immature. One dead infant was delivered by cesarean section, the indication being previous cesarean section and severe pre-eclampsia. (Here again, toxemia and diabetes may explain the largest proportion of deaths of infants who died in utero.)

2. *Died During Delivery.*—Two infants died during delivery. One was a 5,650-gram infant delivered by breech extraction. Shoulders became impacted in the pelvis and the infant was delivered after 10 minutes of hard traction. The other infant who died during delivery weighed 3,610 grams and was delivered by rapid breech extraction because of a prolapsed cord. Autopsy findings indicate that both deaths were due to trauma.

3. *Died Post Partum.*—Nine infants died post partum. Three can possibly be attributed to traumatic delivery. One infant weighed 4,860 grams. The head delivered spontaneously but the large shoulders became impacted in the pelvis and great traction was necessary for delivery. The infant was in poor condition and expired after eight hours. A second infant weighed 3,070 grams and was delivered by high forceps because of face presentation and evidence of fetal distress. The forceps operation was moderately difficult. A third infant weighing 3,240 grams was delivered with difficulty by high forceps because of maternal exhaustion resulting from seventy-four and one-half hours of labor. The infant died post partum. A fourth infant was delivered by cesarean section, the indication being an excessive-sized infant in a severe diabetic. The infant died on the second postpartum day with clinical findings of erythroblastosis fetalis,

Comparing the two groups of diabetic gravid patients, it is apparent that fetal deaths occurred in both, not particularly related to the severity of the diabetes, as judged by the need for insulin. Of the total group of 53 patients *not requiring* insulin, 12 patients lost their infants, an incidence of 22.6 per cent, while the infant mortality in the group of 78 whose diabetes was obviously of greater severity because they needed insulin was 25.6 per cent. This includes immature, premature, and mature infant deaths.

TABLE VIII. FETAL DEATHS

	INTRAUTERINE DEATHS							
	500-1,500 GRAMS IMMATURE		1,500-2,500 GRAMS PREMATURE		2,500 GRAMS MATURE		DIED DURING DELIVERY		
	WEEK DIED IN UTERO	NO.	WEEK DIED IN UTERO	NO.	WEEK DIED IN UTERO	NO.	WEEK OF GESTATION	NO.	NEO-NATAL DEATHS
53 Patients on diet alone	38 26		36		39 38 36 39		43		
No of fetal deaths		2		1		4		1	4
78 Patients on inslulin and diet	36 26		29		35 32 35 35 30 45		36 36		
No. of fetal deaths		2		1		6		2	9
Total deaths		4		2		10		3	13

We are impressed that bouts of keto-acidosis have a definite bearing on the viability of the infant. Seven of the 12 patients whose infants died and who had no evidence of toxemia of pregnancy had bouts of keto-acidosis and insulin reactions during the antenatal course. Three of these patients went into premature labor spontaneously and delivered premature infants which died. Of the remaining 4 patients, 2 lost their infants in utero, and 2 post partum.

Autopsy Findings

Autopsies were performed on most of the dead infants but were of little value in the deadborn macerated infants because of autolytic changes. Significant findings were reported in 13 cases. In this group there were 2 immature, 2 premature, and 9 mature infants.

1. *General Appearance.*—Five infants showed moderate to extensive edema. One was severely jaundiced, one moderately.

2. *Blood Studies Prior to Death.*—Moderate to severe hypoglycemia was present in 5 infants; moderate anemia in 3. Five infants showed more than the average number of nucleated red blood cells per 100 white blood cells.

3. *Lungs.*—Twelve of the 13 infants showed either atelectasis, bronchopneumonia, subpleural or pulmonary hemorrhage, or a combination of the three. Some pathological change in the lung was then the most constant finding.

4. *Heart.*—In 4 infants the heart was enlarged, being described as hypertrophied in two. In one case atresia of the pulmonary valve was demonstrated.

5. *Liver.*—Nine of the infants showed abnormal changes in the liver. In 6, enlargement with fatty degeneration was present, focal necrosis in one, and more than the average number of areas of erythropoiesis in five.

6. *Pancreas.*—The pancreas of 7 of the infants examined showed hypertrophy or hyperplasia of the Isles of Langerhans. Two showed dilatation of the ducts. Acute pancreatitis was demonstrated in one.

7. *Nervous System.*—Eight of the 12 infants showed some form of intracranial hemorrhage. In 2 infants tentorial tears were demonstrated.

Comment

In our group there was a fetal mortality of 21.4 per cent, which must be compared with the results of others. Lawrence and Oakley[10] reported a fetal death rate of 23 per cent; Bill and Posey,[1] 27 per cent; Paton,[15] 26.3 per cent; Palmer,[14] 40 per cent; Lavietes,[9] 39.0 per cent; and White[22] showed a fetal mortality of 17 per cent in 300 consecutive cases carried past the twenty-fourth week of pregnancy. In a general way, our results compare favorably with others. However, when White's[22] data are broken down it becomes clear that she has been able to obtain a fetal survival of 97 per cent in a certain group—that is, the group with a normal hormonal balance. She has also corrected the hormonal balance in a group of 174 patients and was able to reduce the infant mortality to 10 per cent. In addition to hormonal therapy, about 85 per cent of her patients were delivered by cesarean section. These results are superior to ours, and since our approach to the problem has been different in respect to (a) management of the diabetes, (b) time and mode of delivery, and (c) the use of hormone replacement therapy, it is pertinent to inquire which of these factors, individually or in combination, affect the total mortality rate.

1. *The Diabetes.*—Since 1939 we have managed our diabetics by the clinical method, prescribing a generous self-selected diet and enough protamine insulin, or a mixture of regular and protamine in a 2:1 ratio as a single injection in the morning, to maintain the patient by the criteria outlined above. By this method no attempt was made to maintain the urine free from sugar or a normoglycemia. It may therefore be stated that stricter or chemical control might have given us better results. The available evidence does not bear this out. Our results differ very little from those of others, with the exception of White's. All other workers treated the diabetes by the chemical technique. And, if White's results are compared with ours when she did not employ any hormonal therapy, and delivered 50 per cent of her patients by cesarean section during the years 1925 through 1937, it will be seen that she reported a fetal mortality rate varying between 25 per cent and 38 per cent.[23] It seems to us that if rigid control of the chemical metabolism was the deciding factor, our results would not compare as favorably as they do, and it is difficult to infer that the hyperglycemia has a bearing on the viability of the infant.

It may also be believed that chemical control is preferable because:

1. It is conducive to a normal-sized infant.
2. It is less likely to lead to toxemia of pregnancy.
3. It is less likely to contribute to the development of keto-acidosis.

There is no evidence that a high blood sugar is conducive to an oversized baby and there is considerable evidence against this hypothesis. White,[22] Palmer,[14] and others attempted to maintain normal blood sugars and yet large babies were observed. Also, large babies are born to prediabetic mothers in whom no glycosuria, nor hyperglycemia were demonstrated at the time the large infant was born.

The incidence of toxemia among gravid diabetics is high. Paton[15] reports an incidence of 50 per cent; White,[23] 30 to 50 per cent when no hormones were used; in our series there was an incidence of 46 per cent. Here

again the evidence is lacking that hyperglycemia may be a contributing factor as the incidence rates approximate each other rather closely. If hyperglycemia were a contributing factor, the incidence of toxemia should have been higher in our series. This was not borne out by fact.

That a high blood sugar predisposes to keto-acidosis is now a discarded hypothesis. Most observers agree that failure to take insulin, infection, or a combination of the two are the factors responsible for the development of keto-acidosis. In our series, 20 patients were hospitalized during their antepartum course because of keto-acidosis. The acidosis required emergency therapy. Two patients were in coma. It is of note that 11 of the 20 had severe infections which no doubt were the precipitating factors in the development of the keto-acidosis. No apparent cause for the ketosis was found in the remaining nine patients. It is likely that the management of the diabetes, even by the clinical criteria, was faulty in these patients. It is one of the guiding principles to aim at a ketone-free urine. To accomplsh this, adequate amounts of insulin must be given and we were in error in not pushing the insulin until the ketonuria cleared. This circumstance, as well as statements above, point to an insulin insufficiency rather than hyperglycemia as the underlying factor of ketogenesis.

From the above it would seem that the type of diabetic control—clinical or chemical—has no particular bearing on the size of the baby, the incidence of toxemia, and the frequency of keto-acidosis. This view is also shared by Lavietes and his associates,[9] and Paton.[15]

Substitutional Hormonal Therapy.—White[22] has stated that the most important single factor contributing to the high fetal mortality "appears to be the distribution of the sex hormone." It can be said that failure to use sex hormones may explain our comparatively high infant death rate, yet Palmer's[14] results are only slightly better than ours though such hormones were used. We recognize that Palmer's regimen for hormone replacement differed from White's in its duration.

The studies of Smith and Smith[18] have suggested that in toxemia of pregnancy there occurs an alteration in the metabolism of estrogen and progesterone. Specifically, the estrin in the serum is reduced, the pregnandiol excretion in the urine is lowered, and the chorionic gonadotropin of the serum rises. With this Taylor agrees, however, Taylor[20] has not been as successful in treating toxemia of pregnancy with replacement therapy. White has been a strong proponent of replacement therapy as she is of the opinion that the diabetic woman, in whom there often occurs a hormonal imbalance, has little chance of correcting it spontaneously, and therefore, is a candidate for toxemia when pregnant. Furthermore, the presence of toxemia reduces the chances for a viable infant. Consequently, she has used stilbestrol and Proluton to correct this imbalance and has reduced the infant death rate to 10 per cent. Others using replacement therapy have not had the results that in any way approximate White's. Palmer and his associates[14] report a fetal mortality of 16.7 per cent. Jordan[7] reports mortality, both fetal and neonatal, in a series of 33 pregnancies of 39 per cent. Jordan began by administering stilbestrol and progesterone at the beginning of the sixth month of pregnancy. He was guided as to dosage by studying the concentration of gonadotropin in the blood. This he determined at intervals of two weeks. He did not do cesarean sections. Were hormone replacement the only therapy, its evaluation would not be as difficult. But in addition to hormone therapy, White[22] has recommended premature delivery, at the end of the thirty-seventh week or early part of the thirty-eighth week, in many cases by cesarean section. The combined technique makes the evaluation of these procedures, separately, difficult. If the crux of the matter is a hormonal imbalance and this is corrected, why the need

for a premature delivery? One would expect that the correction of the abnormality would be conducive to a normal-sized infant and thus obviate the necessity for a section. However, that is not the case as even with the hormone therapy the babies are still large, and, furthermore, many women who are predestined to diabetes bear large infants some years before their diabetes becomes clinically apparent. This is an established observation and has recently been well documented by Kriss and Futcher.[8] Of course, it may be argued that a hormonal imbalance is present in such individuals but has not been demonstrated because no studies were done. If, however, a hormonal imbalance predisposes to toxemia of pregnancy, one can judge from the frequency of its association with large infants whether not not such an imbalance might have been present. No such correlation can be demonstrated.

Premature Termination of Pregnancy

It seems that cesarean section has resulted in a decreased infant mortality. Randall[17] reports a 96.2 per cent survival of infants delivered by cesarean section, whereas only a 62.5 per cent survival rate was noted when vaginal delivery was the method of choice. It is pertinent, therefore, to inquire whether or not it is this procedure alone that has made childbearing so much more hopeful for the pregnant diabetic. Our data point in such a direction. Had we been less conservative and performed more sections, our infant mortality would have been reduced materially as most of our deaths occurred after the thirty-fifth week and some died at delivery as a result of operative trauma.

There are three pertinent questions to be answered: (1) Is cesarean section preferable to induction and vaginal delivery? (2) Should all diabetic mothers be delivered before term? (3) At what week should delivery be accomplished in those cases where premature delivery is indicated.

Cesarean section affords a means of terminating the pregnancy at an *elective* time, eliminating the hazards of trauma which may occur during the vaginal delivery and accomplishing delivery before intrauterine death may occur. Our data, however, do not clearly support the contention that it is cesarean section in every case rather than the premature delivery per se, that results in a lower infant mortality. Certainly, in those cases where conditions for induction are ideal, where the patient has an adequate pelvis and the infant is not of excessive size, induction and vaginal delivery are indicated. If induction fails and delivery is imperative, cesarean section can be resorted to. Our data indicate, however, that should the labor be prolonged or the delivery difficult, cesarean section should be the procedure of choice. Some maintain that such a hypothesis is not tenable as a section is being performed for an infant potentially abnormal in behavior and structure, who may die regardless of the mode of delivery. With the development of the premature nursery, improved methods of care, greater understanding of the abnormalities of the diabetic infant, the neonatal mortality has declined steadily. During the last three years considered in this study there has not been a single neonatal death of a mature infant of a diabetic mother. The rate for death in utero, however, has remained constant. It is for this group that premature delivery by induction or cesarean section might offer better results (Fig. 10).

Should all pregnant diabetics be subjected to premature delivery? It is obvious that one cannot be dogmatic, yet it appears desirable to propose some guiding principles. If the patient shows no symptoms of diabetes, no excessive gain of weight, no evidence of toxemia, and does not have an excessive-sized infant, she should be allowed to go into labor spontaneously and be delivered vaginally; if the labor is poor, or complications develop, termination of the pregnancy by cesarean section is advised.

What are then the indications for premature delivery? (1) Toxemia, (2) frequent attacks of keto-acidosis, and (3) large infants.

Toxemia.—There were 60 patients with toxemia and 17 of these lost their infants. The great majority of these died in utero after the thirty-second week. The only positive finding that might account for these deaths was the toxemia. In the past we have made costly errors by temporizing with the pregnant diabetic with pre-eclampsia. We are of the opinion, for these reasons, that this type of patient should be delivered at the first sign of toxemia, regardless of the week, if the infant is considered viable. In this connection it is well to relate that with edema of the anterior wall and with excessive amounts of amniotic fluid, the estimation of the size of the infant is often considerably under the actual weight. In view of our experience we place much emphasis on the calculated duration of pregnancy and do not hesitate to do a cesarean section under these circumstances if the pregnancy has reached the thirty-second week.

Keto-acidosis.—In those cases where the diabetes has been complicated by bouts of keto-acidosis, even though toxemia is not present, premature delivery is recommended for it appears that these diabetic patients run a great risk of losing their infants in utero, usually after the thirty-second week.

Large Infants.—A recent survey of all infants weighing over 4,000 grams, delivered from 1932 through 1948, has just been completed.[13] There were 756 such infants; the infant mortality rate among this group was 5.82 per cent, twice the clinic rate. The incidence of diabetes among the mothers of these large infants was 2.27 per cent or *9 times* the clinic incidence as a whole.

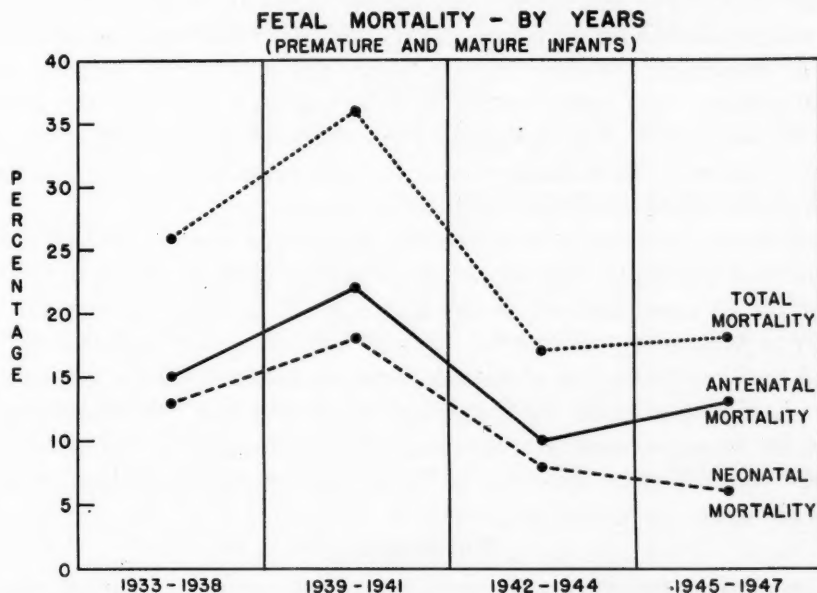FETAL MORTALITY - BY YEARS
(PREMATURE AND MATURE INFANTS)

Fig. 10.

Thirty-three of the infants of diabetic mothers weighed between 4,000 and 5,000 grams. Five, or 13 per cent, of these were lost. Of the 6 infants weighing between 5,000 and 6,000 grams, 3, or 50 per cent, were lost. Our major error was in underestimating the size of these infants, and whereas spontaneous delivery of the head occurred in most cases, shoulder impaction followed, which necessitated great traction for delivery. In 6 instances infant death was the result of trauma of delivery. These probably would have been

saved had we done cesarean sections. Certainly where there is any doubt as to the excessive size of the infant, section should be performed.

We believe that x-ray offers considerable help in estimating the infant size. Further, edema of the infant may be diagnosed by a halo surrounding the head, body, and sometimes small parts.

Summary

A review of 106 patients with 131 pregnancies complicated by diabetes has been presented. Past history of the multigravid patients indicated that the infants of the prediabetic mothers tended to be larger than average. The pregnancy of 75 per cent of the patients terminated after thirty-six weeks. Weight gain was not excessive in general for those patients who registered in the first and second trimesters, but was excessive in two-thirds of the patients who registered in the last trimester. Toxemia was present in 46 per cent of the pregnancies, keto-acidosis in 16.8 per cent.

The diabetes was treated by the clinical technique. There was no constant diminution of insulin requirements observed during pregnancy. Labor was prolonged in 26 per cent of our primigravid patients and in 1.3 per cent of our multigravid patients. Incidence of forceps was 10 per cent, of cesarean section, 9.9 per cent. The sections were performed for obstetrical indications. Maternal mortality was 1.5 per cent, represented by 2 patients, in neither of whom was the diabetes the initiating cause of death. Maternal morbidity was 17 per cent. The infants were routinely sent to the pediatric premature nursery where incubation, oxygen, suction, and dehydration formed the initial regimen of treatment. Thirty and six-tenths per cent of the infants weighed over 4,000 grams. The infant mortality rate was 21.4 per cent, the total fetal loss was 30 per cent.* The severity of the diabetes did not affect the infant mortality. Toxemia, keto-acidosis and the excessive size of the infant were the factors most often associated with infant death.

Errors were often made in estimating the size of the infant and death resulted from the traumatic delivery of impacted shoulders. We believe that delivery should be accomplished at the first sign of developing toxemia, if the pregnancy is past thirty-two weeks. Further, the patient who has been poorly controlled and has had bouts of keto-acidosis should be delivered prematurely. Delivery should be effected by induction of labor when conditions are ideal, otherwise by cesarean section. In the patient with a large infant, or in the case where there is some question as to the size, cesarean section is the procedure of choice.

Conclusions

1. The clinical technique (Tolstoi) for the treatment of diabetics may be applied to the management of the pregnant diabetic.

2. There is no evidence that hyperglycemia, a usual concomitant of this method, is a contributory factor to: (a) the large infant, (b) the greater incidence of toxemia, (c) the episodes of keto-acidosis, and (d) the infant mortality.

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*This included 10 spontaneous abortions, 4 therapeutic abortions, 4 immature infant deaths and ectopic pregnancy.

3. The pregnant diabetic requires rigid supervision by both obstetrician and internist and immediate hospitalization is advised for acidosis, infection, and toxemia. Routine hospitalization at the thirty-fourth week for complete evaluation and decision as to time and mode of delivery is recommended.

4. Intrauterine death of the fetus is most often associated with toxemia and keto-acidosis. Premature delivery for the patients with toxemia and those subject to keto-acidosis is recommended. Delivery should be accomplished by induction and vaginal delivery when possible. Should induction fail, or labor become desultory and prolonged, cesarean section is advised.

5. Recent advances in pediatric care have reduced the neonatal mortality and infant survival is possible even when delivery is effected as early as the thirty-second week.

6. The excessive-sized infant presents a special problem in that accurate estimation of the weight of such infants is subject to more than the usual error. The tendency to underestimate the weight of these infants may be influenced further by anterior abdominal wall edema and an unknown amount of amniotic fluid. Impaction of the shoulders is a major complication in delivery. Cesarean section is recommended for infants estimated to weigh more than 4,500 grams.

7. Water retention in the infant, as evidenced by a halo sign on x-ray, is an indication for immediate delivery, provided the infant is alive.

8. Our observations indicate that hospitalizaton and premature delivery in the complicated case will reduce materially the infant mortality.

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COMPLETE ABDOMINAL HYSTERECTOMY*

A Simplified Technique and End Results in 500 Cases

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I N RECENT gynecological literature there are many reports on the results of hysterectomy. From these reports one must conclude that it is a relatively safe procedure and that there is now little difference in incidence of mortality and morbidity following the subtotal and total operations by the abdominal route. In the hands of competent surgeons mortality for each operation ranges from a fraction of 1 per cent to less than 2 per cent.

Statistics published by some surgeons suggest that complete hysterectomy can be done more safely than the subtotal operation. This can probably be explained by the fact that patients upon whom subtotal operations are done include a higher proportion in whom technical difficulties are encountered and also more women who are known to be poor surgical risks.

The advantages of removing the cervix as well as the body of the uterus in women who have indications for hysterectomy are that:

1. Troublesome postoperative pelvic symptoms caused by chronic cervicitis are eliminated.

2. An occasional unsuspected early carcinoma of the cervix is removed.

3. The risk of subsequent development of cervical malignancy is prevented.

4. Postoperative menopause symptoms are relatively less frequent and less severe than after the subtotal operation and patients adjust more readily to such symptoms when they do occur.

Studies have shown that approximately 85 per cent of women who have indications for hysterectomy will also have cervices with chronic inflammatory lesions or unhealed birth injuries or both. In a recent article, Masson[1] states his belief that ligation of uterine vessels during removal of the uterine body interferes with normal blood supply to the cervical stump and thereby predisposes to development of infection and degenerative changes in the cervical glands. Some cervices which seem fairly normal at time of operation will not always be as near normal when observed in the follow-up. Following subtotal hysterectomies many patients will complain of varying degrees of leucorrhea, pelvic pain,

backache, and dyspareunia. These symptoms are, as a rule, caused by chronic inflammation in the retained cervices. After complete hysterectomy, patients are remarkably free of any of these complaints.

It has been reliably estimated that 1 to 2 per cent of all women will eventually develop carcinoma of the cervix. It has been suspected but not proved that unhealed birth injuries and chronic inflammatory lesions of the cervix predispose to malignant growths. Te Linde[3] reports that four carcinomas were found by serial sections of 300 unsuspected cervices removed when total hysterectomies were done, an incidence of 1 plus per cent. At the Woman's Hospital 6 to 7 per cent of all cervical carcinomas which come under treatment originate in cervical stumps following subtotal hysterectomies. Some may have been present when the hysterectomies were done. Others probably developed later. Te Linde[4] has reported also on a small series of noninvasive carcinomas in women whose average age was 36 years, that is, ten years earlier than the average age for development of gross evidence of cervical carcinoma. His experience has suggested to him the possibility that uterine carcinoma in some women may have a latent period for as long as ten years before manifesting itself. There can be no doubt that removal of the cervix at the time a hysterectomy is done will eradicate an occasional early carcinoma before there is any evidence of its existence as regards symptoms or physical findings.

For every condition which can be cured by surgery it seems that we now have more than one operation or at least many variations in technique. It is through follow-up studies that surgeons are able to select procedures which give the best anatomical results and those which, through freedom from postoperative symptoms, are most satisfactory to patients. It is by such means that some gynecologists have come to realize that, after complete hysterectomy, menopause symptoms are relatively less frequent and less severe, and that time required to adjust to such symptoms is less than after the subtotal operation. The greater frequency of postoperative menopause symptoms after subtotal hysterectomy and the prolonged adjustment to such symptoms have been attributed to a continued reaction between ovarian hormones and endometrium in the retained cervix. From our experience with complete hysterectomy we are convinced that postoperative menopause symptoms which occur can usually be relieved by one of the standard estrogen tablets taken before retiring. Furthermore, substitutional therapy is, as a rule, required for only a short time, if at all, after operation. It is satisfactory to be able to assure women who need hysterectomy that postoperative symptoms of artificial menopause are unlikely to occur or can be easily controlled. From a patient's standpoint a postoperative course relatively free of menopause symptoms means a great reduction in physical discomfort to say nothing of the psychological benefit which she derives from the conviction that she has not been suddenly converted to an asexual being.

Convinced of the advantages of total abdominal hysterectomy, various techniques have been tried at the Woman's Hospital in an effort to find one which could be safely used as nearly a routine procedure. It seemed obvious that such an operation must be one which:

1. Was technically as simple as possible.
2. Would afford maximum protection against injury to the bladder, ureters, and rectum.

3. Could be done with a minimum of trauma to structures about the vaginal vault and to their blood supply.

4. Would leave the vagina normal as to depth and the vaginal vault well supported and elastic.

5. Was simple enough to be taught to members of our resident staff.

The technique which was finally adopted will be described. No priority is claimed for any step in this procedure. It is simply a combination and modification of various steps which have been described previously by Worrall,[5] Richardson,[6] Danforth,[8] Farrar,[7] Masson,[2] and others in techniques for subtotal and complete hysterectomy. It has now been used by members of the Woman's Hospital Staff for 500 complete hysterectomies in women who have been followed long enough to be certain of final results. We believe that in practice it has met the objectives outlined above in that it has proved to be a relatively simple, safe procedure which can be used almost routinely for complete removal of the uterus whenever there is an indication for hysterectomy.

Procedure

Preoperative preparation of the patient consists of shaving and careful cleansing of the skin of the vulva and abdomen and a vaginal douche. After the patient has been anesthetized, the vulva and vagina are thoroughly cleansed with green soap and water and the vagina is carefully painted with tincture of Zephiran.

Figs. 1 to 4 inclusive show various steps in the technique which has been used.

In Fig. 1, it will be noted that exposure of the operative field has been accomplished by means of a Pfannenstiel incision and an O'Sullivan-O'Connor retractor. The original steps carried out in the operation are the same as for any standard subtotal hysterectomy. The proximal ends of round, uteroovarian and broad ligaments, and the Fallopian tubes are detached from the lateral surfaces of the uterus and, if indicated, the tubes and ovaries are removed. The uterovesical fold of peritoneum is incised and the bladder is displaced downward only to the extent necessary for fairly low supravaginal amputation of the uterine corpus. The uterine blood vessels, U.V., are clamped, cut, and ligated on each side about 1.5 cm. above the fornix of the vagina. Sutures used to ligate the uterine vessels are temporarily retained for traction.

Subsequent steps in the operation depend upon the fact that the uterus is supported at a normal level in the pelvis by the transverse cervical ligaments. These dense, musculofascial structures known also as the cardinal or Mackenrodt's ligaments, are located in the base of each broad ligament. They extend from the walls of the pelvis to the lateral surfaces of the cervix. Continuous with these ligaments and as a part of the same supporting fascial system, there is a dense, thin layer of connective tissue which completely surrounds the lower segment of the uterus, the cervix and the vault of the vagina. After downward displacement of the bladder this fascial structure can be readily recognized as a smooth, glistening layer of tissue on the anterior surface of the cervix. On the posterior surface of the cervix, it is covered by a layer of parietal peritoneum.

In Fig. 1, it will be noted that the peritoneum and layer of fascia described above have been opened with a superficial incision extending between the two points at which the uterine vessels, U.V., were ligated and just above the proximal ends of the uterosacral ligaments. The margins of the incised peritoneum and

fascia have been picked up with Allis clamps, 1, and the incised fascial cuff, F.C., is being separated from the posterior surface of the cervix with blunt-nosed scissors. It will be noted that the proximal ends of the uterosacral ligaments are not ligated and cut but are displaced backward as the fascial cuff, F.C., is detached from the posterior surface of the cervix. This step in technique is also helpful at times when the large bowel is fixed to the anterior surface of the cul-de-sac by dense adhesions resulting from healed inflammation or endometriosis. In such circumstances, the adherent bowel can be displaced with the fascial cuff, F.C., thereby avoiding troublesome bleeding and the risk of bowel injury.
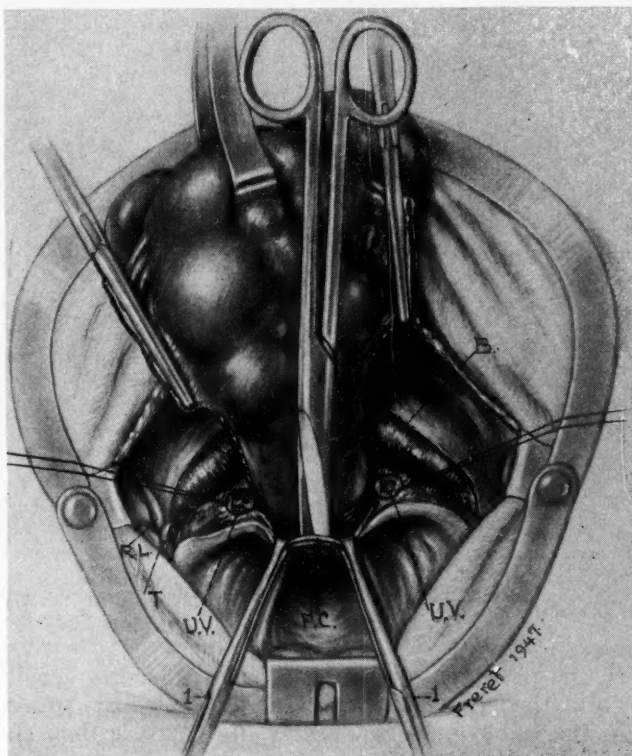

Fig. 1.—Dissection of fascial cuff, F.C., from posterior surface of cervix. B., Bladder. U.V., Ligated uterine blood vessels.

Fig. 2, *A* shows the incised fascial layer, F.C., being separated from the anterior surface of the cervix. The incision is made at the same level as that on the posterior surface of the cervix, Fig. 1, and about 2 cm. above the margin of the displaced bladder, *B*.

Fig. 2, *B* is a cross section of the cervix and vault of the vagina showing the approximate location of the fascial cuff, F.C., which has been dissected off the surfaces of the cervix and adjacent wall of the vagina. The margins of the cuff are being retracted with Allis clamps, 1 and 2.

In Fig. 3, *A*, the right transverse cervical ligament, T.C.L., has been clamped with a Kocher clamp between the ligated uterine vessels, U.V., and lateral surface of the cervix. Placement of this clamp is facilitated by gentle traction on the suture used to ligate the vessels, U.V., and Allis clamps to retract the margins of the fascial cuff, F.C. It will be noted also that the tips of the clamp are inside the fascial cuff, F.C., which surrounds the cervix.

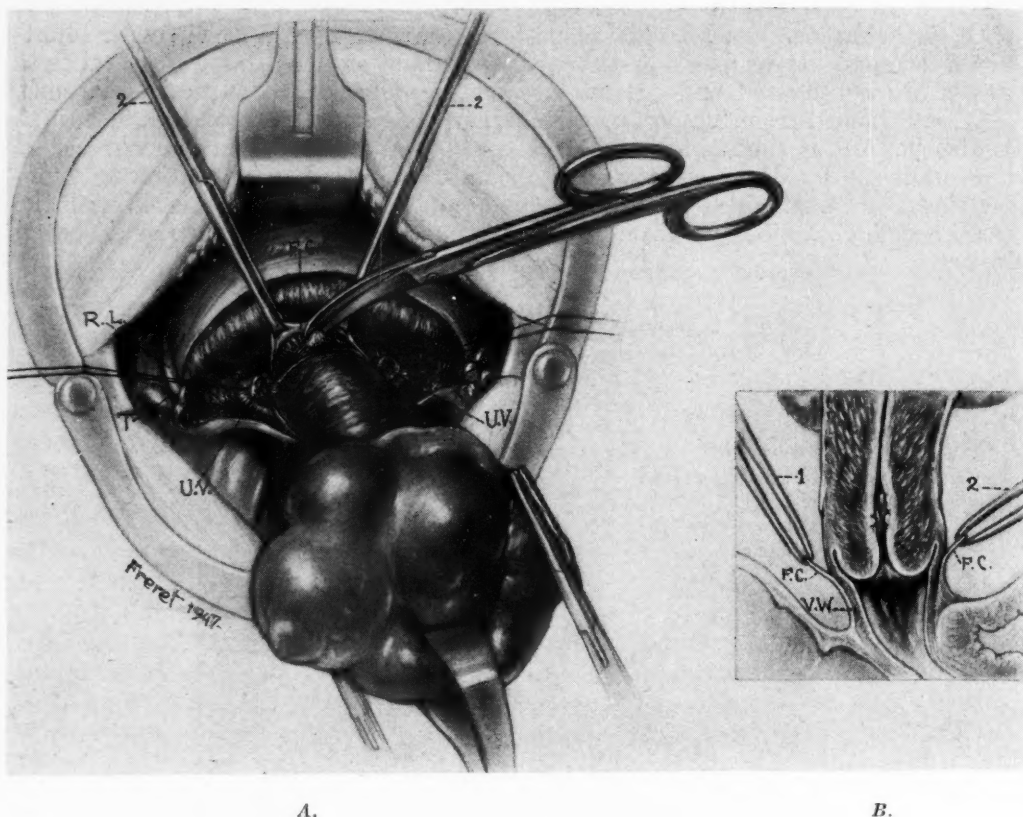A.   B.

Fig. 2.—A, Dissection of fascial cuff, F.C., from anterior surface of cervix. U.V., Ligated uterine blood vessels. B., Bladder.

B, A cross section showing the approximate location of the fascial cuff, F.C., in relation to cervix and wall of vaginl vault. V.W., Wall of vagina.

In Fig. 3, B, the proximal end of the right transverse cervical ligament has been detached from the cervix and is being ligated. By procedures shown in Fig. 3, A and B, the left transverse cervical ligament is then clamped, cut, and ligated in the same manner as the right.

Steps shown in Fig. 3, A and B, are important in that ligation and detachment of the transverse cervical ligaments are carried out within the fascial cuff, F.C., where there is no risk of injury to adjacent structures and especially the ureters.

After the transverse cervical ligaments have been detached, the cervix can be readily drawn upward by firm traction on the body of the uterus. A bit more dissection within the fascial cuff may be necessary before the cervix can be released from the vaginal vault by steps shown in Fig. 3, C, D, and E.

Fig. 4 shows steps used for closure of the vaginal vault and peritonization of all raw surfaces.

Fig. 4, A shows the placement of four sutures, 1, 2, 3, 4, in the margins of the vaginal wall. In the fornices of the vagina. sutures 1 and 3 are passed through the mucosa and wall of the vagina, V.W., around the ligated stumps of the transverse cervical ligaments, a, and back into the vagina where they are tied. The importance of these angle sutures is that they help to control bleeding and also that they provide additional support to the vagina by fixing the proxi-
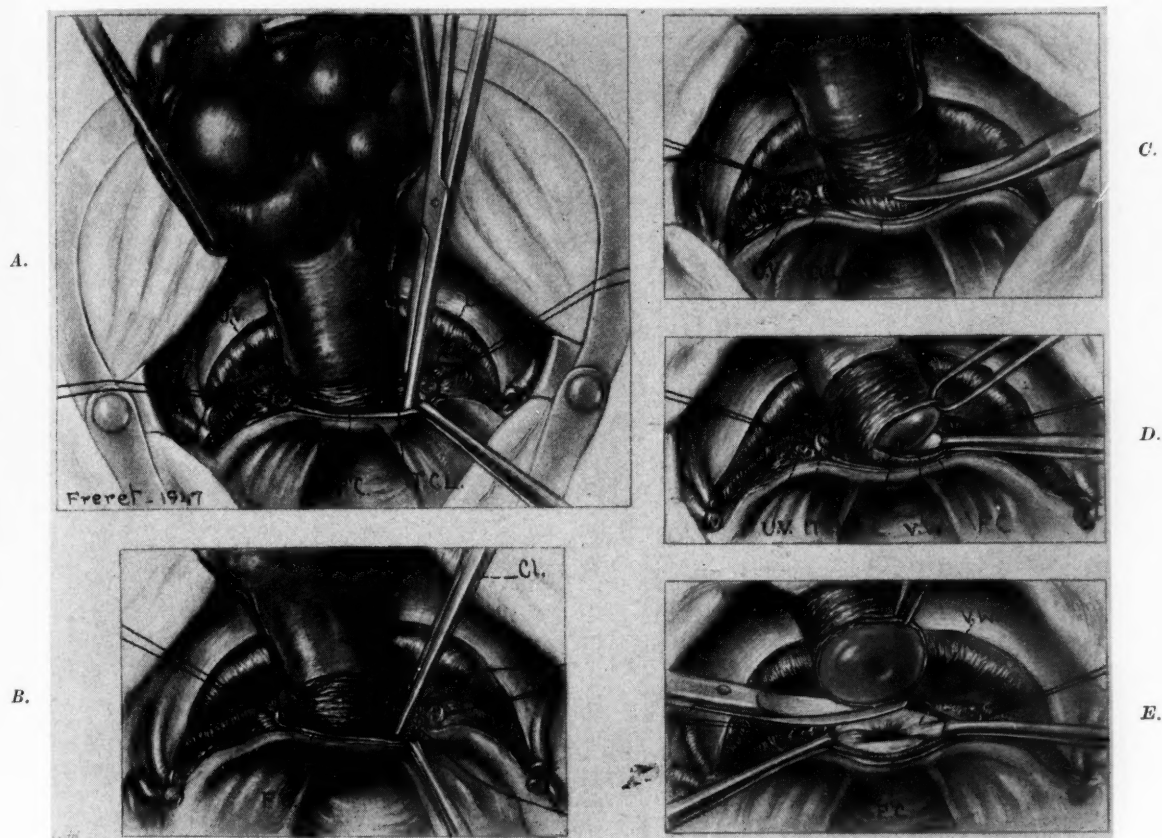
Fig. 3.—*A*, Placement of Kocher clamp on right transverse cervical ligament, T.C.L., be-
tween cervix and ligated uterine vessels, U.V., and inside fascial cuff, F.C.

B, Ligation of right detached cervical ligament.

C, *D*, and *E*, Excision of cervix from vaginal vault, V.W. C., Cervix. T.C.L., Trans-
verse cervical ligaments. U.V., Uterine blood vessels. F.C., Fascial cuff.

mal ends of the transverse cervical ligaments, a, to the vault. Two more traction
sutures, 2 and 4, are passed through the mucosa and wall of the vagina in the
midline.

In Fig. 4, *B*, the vault of the vagina is being closed with a running suture
of No. 0 chromic catgut. This suture includes the mucosa and wall of the vagina,
V.W., but not the fascial cuff, F.C., described above. Closure of the vault is
facilitated by gentle traction on the four sutures, 1, 2, 3 and 4, shown in Figs.
4, *A* and 4, *B*. At this stage of the procedure it is unnecessary to have any
clamps in the pelvis.

Some surgeons believe that healing of the vaginal vault will be better if it
is closed with a running submucous suture. This can be easily done as a part
of this procedure. However, we are convinced that unsatisfactory healing of
the vault following some of the older techniques for complete hysterectomy was
due to unnecessary interference with blood supply to structures about the vault.
An advantage of the technique described above is that a minimum of trauma
is required to release the cervix from the vault of the vagina. In other words
protection of blood supply to the vault may be more important for healing than
the method by which it is closed.

In Fig. 4, *C*, it will be noted that the fascial cuff, F.C., described in Figs.
1, 2, and 3, is being closed over the vaginal vault with another running suture

A.   B.

C.   D.
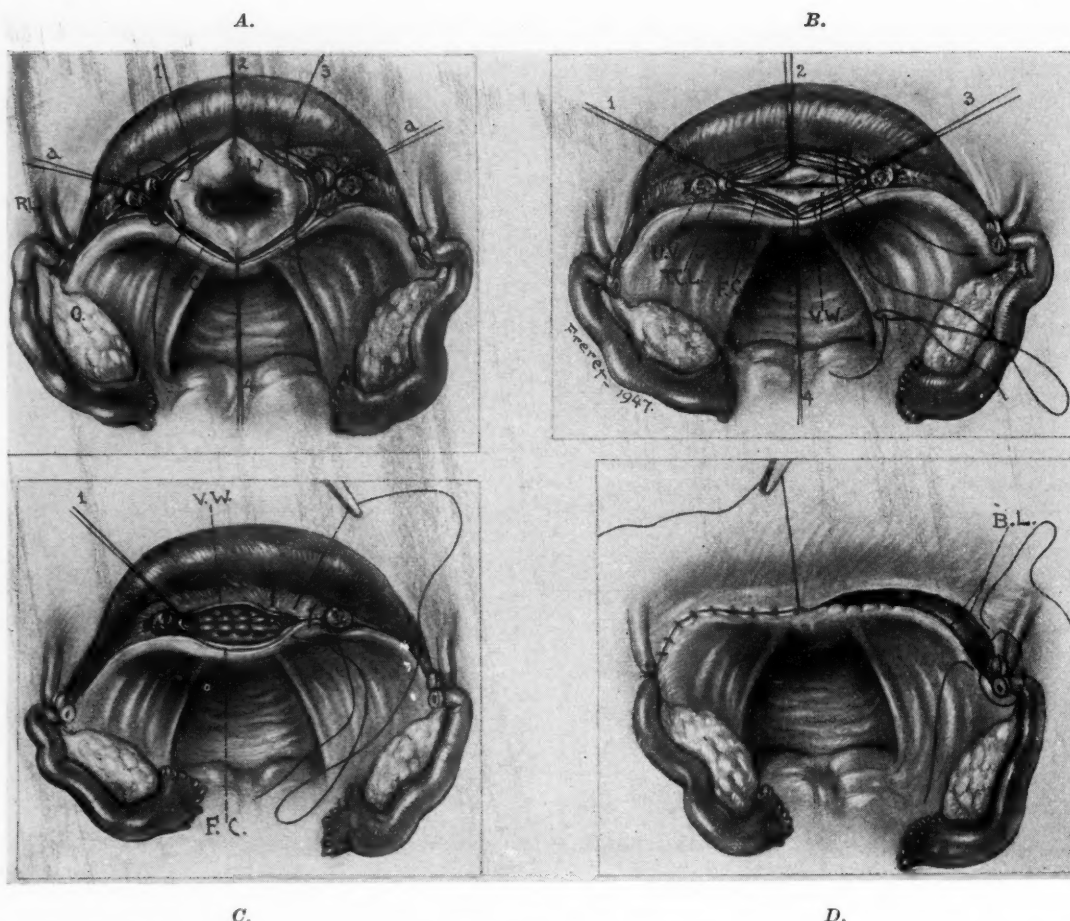
Fig. 4.—*A*, Placement of sutures 1, 2, 3, and 4 in vaginal vault. Sutures 2 and 4 are for traction. The detached uterine ends of transverse cervical ligaments are fixed to the fornices of the vagina by sutures 1 and 3.

B, Closure of mucosa and muscular wall, V.W., of vagina with a running suture of No. 0 chromic catgut.

C, Closure of fascial cuff, F.C., over vault of vagina, V.W., with No. 0 chromic catgut.

D, Peritonization of raw surfaces.

of No. 0 chromic catgut. In closing the fascial cuff, the proximal ends of the uterosacral ligaments are brought back into normal position.

Fig. 4, *D*, shows peritonization of all raw surfaces. Using plain catgut it is started as a purse string which picks up the margins of the broad ligament, B.L., and surrounds the pedicles of the tube, uteroovarian and round ligaments. The suture is then tied and continued to the midline as a running suture. After the same procedure has been carried out on the opposite side, the ends of the two peritonizing sutures are tied together in the midline. The proximal ends of the broad, round, uteroovarian or infundibulopelvic ligaments are never fixed to the vaginal vault to facilitate peritonization or as a means of support for the vagina. We believe that such a procedure is unnecessary and that these ligaments when fixed to the vault provide little if any support. Furthermore, we believe that blood supply to the ovaries is improved by permitting them to be retracted to the lateral walls of the pelvis as shown in Fig. 4, *D*. When the ovaries are drawn toward the midline they tend to prolapse into the cul-de-sac causing postoperative pain and dyspareunia.

Fig. 5 shows a modification in technique for closing the vaginal vault in patients in whom it is obvious that the vault is poorly supported. In Fig. 5, *A*,

it will be noted that the mucosa and wall of the vagina, V.W., are being closed with a running suture, S1, from side to side rather than in an anteroposterior direction as shown in Fig. 4, *B*. Fig. 5, *B* shows closure of the fascial cuff, F.C., from side to side rather than anteroposteriorly as shown in Fig. 4, *C*. In Fig. 5, *C*, raw surfaces are being peritonized by the same method as shown in Fig. 4, *D*. The advantage of steps shown in Fig. 5, *C* is that the proximal ends of the transverse cervical ligaments which have been previously fixed to the fornix of the vagina on each side are brought nearly into apposition in the midline. By this means relaxation of the transverse cervical ligaments is eliminated and better support for the vault is assured.

Steps shown in Fig. 5, *A, B,* and *C* are not recommended as routine procedures as they tend to fix the vaginal vault and to reduce its elasticity. Some patients in whom this occurs will complain of dyspareunia and a shortened vagina.
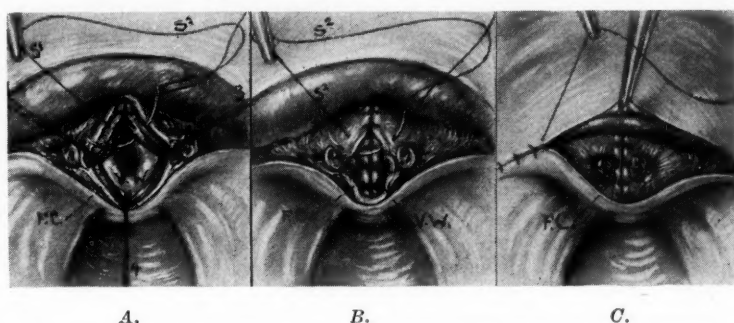
Fig. 5.—Modification of technique for closure of a poorly supported vaginal vault.
A, Closure of mucosa and muscular wall, V.W., of vagina from side to side with suture, S1.
B, Closure of fascial cuff, F.C., from side to side with suture, S2. V.W., closed vaginal wall.
C, Peritonization of raw surfaces.

Steps in this technique for complete abdominal hysterectomy which have contributed to the safety of the procedure and to better results may be summarized as follows:

1. Release of the cervix from the vault of the vagina by dissection within the pericervical fascial cuff, thereby avoiding any risk of injury to the ureters, bladder, or bowel.

2. Effective prevention of hemorrhage by ligation of blood vessels in easily accessible safe areas.

3. Promotion of wound healing by a minimum of trauma to structures about the vaginal vault and to their blood supply.

4. Fixation of the detached proximal ends of the transverse cervical ligaments to the vaginal vault in a way which leaves it well supported and elastic.

5. Elimination of all clamps from the pelvis to facilitate closure of the vaginal vault and peritonization of raw surfaces.

6. Support of retained ovaries near the lateral walls of the pelvis to protect their blood supply and to prevent pelvic pain and dyspareunia from prolapse of the ovaries into the cul-de-sac.

It seems doubtful that a technique can ever be devised by which the entire uterus can be removed quite as easily or as quickly as a subtotal hysterectomy can be done. However, experience with the technique just described has proved

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again that complete removal of the uterus can be safely done as nearly a routine procedure in women who have conditions requiring removal of the uterine corpus. We are now convinced that for nearly all women hysterectomy should mean complete removal of the uterus. A few exceptions will occur in women who have degenerative diseases or physical conditions which leave them a narrow margin of safety if subjected to any type of a surgical procedure. Experience proves that the seriousness of these conditions cannot always be estimated by routine preoperative studies. Symptoms will occasionally develop during induction of anesthesia or in the early stages of an operation to convince a surgeon that no time should be lost in completing the operation which has been undertaken. Subtotal hysterectomy may be advisable for some women as a means of reducing to a minimum the amount of time and anesthesia required for a surgical procedure to relieve their symptoms.

Tables I to VIII, inclusive, are summaries of data regarding a series of 500 complete abdominal hysterectomies done by the Woman's Hospital staff using the technique described above.

TABLE I. DISTRIBUTION OF 500 COMPLETE ABDOMINAL HYSTERECTOMIES DONE BY 23 MEMBERS OF OUR ATTENDING STAFF AND 10 RESIDENT SURGEONS

OPERATIONS PERFORMED BY	NO. OF OPERATIONS
Members of the Attending Staff	300
Resident Surgeons under supervision of members of the Attending Staff	160
Chief Resident in Gynecology	40
Total number of hysterectomies	500

Members of the Resident Staff, alone or under supervision of members of the Attending Staff, did 200 of 230 complete hysterectomies on ward patients, that is, 86.9 per cent.

TABLE II. RECORD OF PREVIOUS OPERATIONS IN THE 500 PATIENTS WHO HAD COMPLETE ABDOMINAL HYSTERECTOMIES

Of the 500 patients, 173 had had previous operations as follows:	
Uterine curettage only	43
Appendectomy only	52
Vaginal or abdominal operations upon pelvic organs	88*
No previous operations	317
Total	500

*Fifty-three of these patients had also had appendectomies.

We are convinced that patients adjust more readily to physiological changes following hysterectomy if normal ovaries are retained. In this series one or both ovaries were left in situ in 315, or 63 per cent, of the 500 patients who had complete hysterectomies. We do not hesitate to remove a diseased appendix at the time a hysterectomy is done. Opinion varies as to the desirability of doing routine prophylactic appendectomies. The appendix was removed at previous operations or at time of hysterectomy in 278, or 55.6 per cent, of the patients who had had hysterectomies.

TABLE III. DATA REGARDING REMOVAL OF OVARIES AND THE APPENDIX IN THE 500 PATIENTS WHO HAD COMPLETE ABDOMINAL HYSTERECTOMIES

	NUMBER OF PATIENTS
Both ovaries retained	167
One ovary retained	148
Both ovaries removed	185
Total number of patients	500

The appendix was removed from 278 of the 500 patients.

A high percentage of the 500 hysterectomies were done for benign pathological conditions of the uterus or as a part of operative procedures for adnexal conditions which required removal of both tubes and ovaries for relief of symptoms.

TABLE IV. SUMMARY OF FINDINGS IN 16 OF THE 500 PATIENTS WHO HAD MALIGNANT TUMORS OF THE PELVIC ORGANS AT THE TIME HYSTERECTOMIES WERE DONE

Malignant Conditions Diagnosed Before Operation.—	
Carcinoma of corpus uteri	7
(Previous diagnostic curettage and radium)	
Carcinoma of ovary	2
Total	9
Malignant Conditions Diagnosed at Time of Operation or by Pathologist.—	
Carcinoma of corpus uteri	1
Carcinoma of cervix	3
(Noninvasive carcinoma 1)	
Carcinoma of ovary	3
Total	7

Gross and microscopic examinations of the cervices removed in the course of the 500 hysterectomies revealed chronic inflammatory lesions, unhealed birth injuries, or malignancy in 429, or 85.8 per cent.

TABLE V. SUMMARY OF POSTOPERATIVE COMPLICATIONS FOLLOWING 500 COMPLETE ABDOMINAL HYSTERECTOMIES

Urinary Tract Infections		8
Cystitis	5	
Pyelitis	3	
Respiratory Infections		5
Upper respiratory infection	1	
Bronchopneumonia	2	
(One in old bilateral pulmonary tuberculosis)		
Reactivation of old bilateral pulmonary tuberculosis	1	
Pleurisy	1	
Pelvic Infections		4
Wound infection	1	
Parametritis	1	
Pelvic peritonitis	1	
Pelvic abscess	1	
Circulatory System		6
Phlebitis	3	
Pulmonary embolus	1	
(Death on 9th postoperative day)		
Cerebral embolus	1	
(Death on 17th postoperative day)		
Hemorrhage into abdominal wound, shock	1	
Gastrointestinal Tract		2
Intestinal obstruction	1	
(Operation to release small bowel adhesions)		
Fistula between small bowel and vagina	1	
(Operation for small bowel resection)		
Miscellaneous		3
Parotitis	1	
Transfusion reaction	1	
Allergy to penicillin in oil and beeswax	1	
Deaths		
2 in 500 cases	0.4%	

As shown in Table IV, 16 of the 500 patients had malignant neoplasms involving the uterus or ovaries or both at the time the hysterectomies were done. Both tubes and ovaries, as well as the entire uterus, were removed from all of these patients. The question may be raised as to whether the technique for

hysterectomy described above permits removal of enough tissue in patients who are known to have carcinoma of the uterine corpus. For such cases it may be wise to adopt a technique by which more of the parametrial tissue and vault of the vagina can be removed as well as the entire uterus.

Of patients operated upon, 5.7 per cent had significant postoperative complications. There were no bladder or ureteral injuries and no postoperative urinary tract fistulas. A serious complication occurred in one woman, Miss C., Hospital number 88583, following removal of the uterus and both tubes and ovaries for fibroids and an extensive endometriosis. An injury to the mesentery of a densely adherent loop of terminal ileum was repaired at time of operation. Subsequent events included an area of necrosis in the injured bowel, a pelvic abscess, and, on the tenth postoperative day, a fistula between the bowel and vault of the vagina. This patient recovered completely after resection of the damaged loop of bowel.

There were two postoperative deaths. One woman, Mrs. C. Y., Hospital number 49630, aged 50 years, died suddenly on the ninth postoperative day of pulmonary embolus. It was known that she had had rheumatic cardiac disease from 18 years of age. Until the time of her death, the postoperative course had been uneventful. The second death occurred in a woman, Mrs. M. A., Hospital number 90649, who had had prolonged treatment for a syphilitic infection. Following operation, she never regained consciousness and died on the seventeenth postoperative day. Autopsy proved that death was due to cerebral arteriosclerosis and a cerebral embolus.

Of the 500 patients who had complete abdominal hysterectomies 495 were followed long enough to be reasonably certain of postoperative results. Tables VI to VIII, inclusive, are summaries of postoperative findings.

TABLE VI. DATA REGARDING HEALING AND SUPPORT OF VAGINAL VAULT

GRANULATION IN VAULT	NUMBER OF PATIENTS
Slight	72
Moderate	8
Extensive	1
Total	81 or 18.1%

3 patients had only fair support of the vaginal vault.

Of the 495 patients followed, 133, or 26.8 per cent, required treatment for postoperative menopause symptoms. The need for treatment was obviously related to the patient's general health. Many patients required no treatment after having regained their physical strength. Again we are convinced that a patient is likely to adjust more readily to postoperative menopause symptoms if the entire uterus is removed and at least one normal ovary is retained.

TABLE VII. DATA REGARDING INCIDENCE OF PATIENTS REQUIRING TREATMENT FOR POSTOPERATIVE MENOPAUSE SYMPTOMS WHEN OVARIES WERE REMOVED OR RETAINED AT TIME OF HYSTERECTOMY

	NUMBER OF PATIENTS	MENOPAUSE SYMPTOMS		
		NUMBER	PER CENT	RATIO
Both ovaries retained	167	25	14.9	1 in 6.7
One ovary removed	148	27	18.2	1 in 5.4
Both ovaries removed	180	81	45.0	1 in 2.2
No follow-up	5			
Total	500			

TABLE VIII. SUMMARY OF FOLLOW-UP FINDINGS AS REGARDS RETAINED TUBES AND OVARIES FOLLOWING COMPLETE HYSTERECTOMY

Of the 495 patients examined, 3.8 per cent had abnormalities of the tubes and ovaries as follows:

Adnexal thickening and pain	5
Adrenal thickening and no symptoms	2
Cystic ovaries with symptoms	7
Cystic ovaries with no symptoms	5
Total	19

Two patients with cystic ovaries had ovarian carcinoma at time of operation and one had pelvic tuberculosis. Two patients had secondary operations for cystic ovaries.

Conclusions

1. We have now techniques for complete removal of the uterus by the abdominal route which in the hands of competent surgeons are as safe as those for the subtotal operation.

2. At least four out of five cervices removed from women who have indications for hysterectomy will show unhealed birth injuries, chronic inflammation, or an occasional unsuspected malignant growth.

3. Complete removal of the uterus as a nearly routine procedure may prevent later development of an occasional carcinoma in a cervical stump.

4. The incidence of postoperative pelvic complaints and the frequency and severity of menopause symptoms are less after complete removal of the uterus than after subtotal hysterectomy.

5. It is logical to choose the subtotal operation for some women who are definitely poor surgical risks.

6. Results from utilization of the technique just described by a group of gynecologists and hospital residents, in a series of 500 cases, have convinced us that it is a simple, safe method for complete hysterectomy. Our experience has demonstrated that it can be readily adapted to varying conditions encountered in patients who have indications for removal of a part or all of the uterus.

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OVARIAN CARCINOMA ARISING IN ENDOMETRIOSIS*

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THE genesis of many forms of ovarian malignancy is obscure. This obscurity is in part due to the fact that the lesion is often widespread before it comes to clinical atention. Its point of origin, therefore, is already overgrown. This difficulty has contributed to the relative lack of substantiation of Sampson's contention that ovarian carcinoma may often arise in endometriosis.[1] Indeed, there are only eight undoubted cases of this type reported in the literature.

Sampson[2] first reported, in 1925, a series of seven cases of ovarian carcinoma which he felt might have originated in endometriosis. He, however, accepted only two of these cases as definite. Novak and Goodall,[3] on the other hand, accepted only one (Case 5) as conforming to the rigid criteria adopted by Sampson himself. These criteria are: (1) "the actual demonstration of both cancer and benign endometrial tissue in the same ovary"; (2) the cancer and benign endometrial tissue must bear "the same relation to each other that cancer of the body of the uterus bears to the nonmalignant portions of the endometrium"; and (3) "it must be shown that the cancer arose in this tissue and that it is not invading it from some other source." We agree that only Case 5 absolutely fits these criteria.

In the past two years a series of reports of cases similar to the one generally accepted case of Sampson's have appeared. Kuzma[4] reported two cases of adenoacanthoma associated with endometriosis, one of which fits Sampson's criteria. Novak[5] has also reported a case of this type in which the transition from benign to malignant epithelium is as clearly demonstrated as in the original case of Sampson. The cases reported by McCullough, Froats, and Falk,[6] and by Moss and Runals[7] likewise appear to represent adenoacanthoma arising in endometriosis. Cases of adenocarcinoma of this origin have been reported by Miller, Grayzel, Schiffer, and Rosenblatt,[8] by Teilum,[9] and by Rauramo.[10] Teilum's case alone among these demonstrates the actual transition from benign endometriosis to adenocarcinoma.

The case reported by Tuthill,[11] on the other hand, does not seem to us to represent malignancy arising in endometriosis, but rather an atypical arrhenoblastoma associated closely with an endometrial cyst.

With the exception of Sampson's original study, all the reported cases represent isolated observations. It occurred to the authors, therefore, that a study of a relatively large series of ovarian carcinomas and ovarian endometriosis might be valuable in attempting to ascertain the histogenesis and relative frequency of malignancy arising in ovarian endometriosis.

Material and Statistics

This study is based on 265 ovarian malignancies and 889 microscopically proved cases of ovarian endometriosis occurring among 90,611 gynecological admissions to the Free Hospital for Women over a 45-year period from 1903 to

1947. Of these admissions, 3,878 were for primary malignant lesions. The emphasis in the present study is, of course, on these cases with ovarian endometriosis. A detailed clinical-pathological study of the ovarian malignancies has been published recently.

The ages of the 889 patients with ovarian endometriosis varied from 20 to 72 years. The average age was 34 years. As can be seen from Table I, the majority of the cases (61.7 per cent) represent endometrial cysts. Associated ovarian neoplasms are relatively infrequent, being found in only 7.9 per cent of the cases. Only 22.9 per cent of these, representing 1.7 per cent of the whole series, are malignant neoplasms. The types and number of each type of benign and malignant ovarian neoplasm are shown in Tables II and III, respectively.

TABLE I. OVARIAN ENDOMETRIOSIS AND ASSOCIATED OVARIAN HETEROPLASIA

ASSOCIATED LESION	TYPE OF ENDOMETRIOSIS		TOTAL
	CYST	NO CYST	
None	505	302	807
Benign ovarian neoplasm	20*	35	55
Malignant ovarian neoplasm	11†	5	16
Anaplasia in endometriosis	6	0	6
Papillary formation in endometriosis	5	0	5
Totals	547	342	889

*Includes one pseudomucinous cystoma arising in endometriosis.
†Includes six malignant neoplasms either probably or definitely arising in endometriosis.

TABLE II. BENIGN OVARIAN NEOPLASMS ASSOCIATED WITH OVARIAN ENDOMETRIOSIS

TYPE OF NEOPLASM	TYPE OF ENDOMETRIOSIS		TOTAL
	CYST	NO CYST	
Cystadenofibroma	7	12	19
Same ovary	(6)	(11)	
Other ovary	(1)	(1)	
Pseudomucinous cyst	5*	5	10
Same ovary	(4)*	(3)	
Other ovary	(1)	(2)	
Serous cyst	2	5	7
Same ovary	(2)	(5)	
Other ovary	(0)	(0)	
Dermoid cyst	3	4	7
Same ovary	(2)	(3)	
Other Ovary	(1)	(1)	
Fibroma	1	5	6
Same ovary	(1)	(4)	
Other ovary	(0)	(1)	
Estrogenic tumor	1	4	5
Same ovary	(1)	(3)	
Other ovary	(0)	(1)	
Leiomyoma	1	0	1
Totals	20	35	55

*Includes one arising in endometriosis.

It can also be seen from Table I that the types of transformation likely to be the precursors of malignancy (i.e., anaplasia and papillary formation) are uncommon, representing only 1.2 per cent of the series. Truly anaplastic epithelium was encountered only six times, and true papillary formations were seen in only five endometrial cysts. On the other hand, six of the malignant ovarian neoplasms and one of the benign neoplasms (a pseudomucinous cystoma) appear to us to have probably arisen in endometrial cysts. The six malignant neoplasms represent 2.3 per cent of the ovarian malignancies associated with endometriosis, but only 0.7 per cent of the total cases of ovarian endometriosis. If one con-

siders the cases of anaplasia and papillary formation together with the definite malignancies, it then appears that definite or potential malignant changes in ovarian endometriosis occurred in 2 per cent of our cases.

TABLE III. MALIGNANT OVARIAN NEOPLASMS ASSOCIATED WITH OVARIAN ENDOMETRIOSIS

	TYPE OF ENDOMETRIOSIS		
TYPE OF NEOPLASM	CYST	NO CYST	TOTAL
Pseudomucinous cystadenocarcinoma	2*	3	5
Same ovary	(2)*	(2)	
Other ovary	(0)	(1)	
Serous cystadenocarcinoma	4†	0	4
Same ovary	(4)†	(0)	
Other ovary	(0)	(0)	
Adenocarcinoma	3†	1	4
Same ovary	(2)‡	(0)	
Other ovary	(1)	(1)	
Adenoacanthoma	1§	0	1
Same ovary	(1)§	(0)	
Other ovary	(0)	(0)	
Mesonephroma	0	1	1
Same ovary	(0)	(0)	
Other ovary	(0)	(1)	
Sarcoma	1	0	1
Same ovary	(0)	(0)	
Other ovary	(1)	(0)	
Totals	11	5	16

*Includes one probably arising in endometriosis.
†Includes one definitely arising in endometriosis.
‡Includes two probably arising in endometriosis and one definitely arising in endometriosis.
§Includes one definitely arising in endometriosis.

Observations and Report of Cases

Histogenesis of Endometriosis.—

In the course of our studies we have encountered nine cases which appear firmly to support the celomic metaplasia theory of the histogenesis of endometriosis. In these cases we have been impressed with the totipotentiality of the germinal epithelium of the ovary. Among them are examples of germinal epithelial elements recapitulating all of the epithelial components of the Müllerian system, i.e., tubal epithelium, endometrial epithelium, and mucus-producing endocervical epithelium.

In the earliest example of this type, typical endometrial stroma surrounds an unmistakable germinal inclusion cyst. In two cases this change has gone further in that a few cystic spaces in an area with typical germinal inclusion cysts are lined with endometrial epithelium and surrounded by endometrial stroma. There are four cases in which endometriosis can be seen arising in cystadenofibromas. The last two cases in this group show several types of epithelium within cystadenofibromas. One of these contains, in addition to undifferentiated epithelium, areas of tubal epithelium and areas of endometriosis. In the other, three different areas in one cyst show, respectively, undifferentiated epithelium, endometriosis, and pseudomucinous, or endocervical, epithelium. It would not seem far-fetched, therefore, to assume from this evidence that serous cysts, pseudomucinous cysts, and endometriosis may all arise from ovarian germinal epithelium.

Although these cases offer evidence with regard to the histogenesis of endometriosis, this is not the primary purpose for presenting them. Rather they are cited as suggesting that other than endometrial type malignancies may arise within primarily endometrial cysts. Two other cases in our series also support this contention. In these an area of pseudomucinous epithelium was found in an otherwise clinically and pathologically typical endometrial cyst.

The evidence suggests that such areas may arise from polydifferentiation of the original germinal epithelium rather than from metaplasia in the areas of endometriosis. However, the latter possibility cannot be absolutely excluded, especially if we are to accept Sampson's theory as explaining the histogenesis of some cases of endometriosis.

Papillary Projections Within Endometrial Cysts.—

It occurred to the authors, as it has to Novak[5] and others, that the study of papillary projections in endometrial cysts might shed light on the origin of malignancy within such cysts. Papillae, however, are rare in material such as ours in which they have not been originally specifically searched for. Indeed, as previously mentioned, we have encountered only five cases in which true papillary projections with blood vessels and other supporting structures can be demonstrated.

Anaplasia in Endometrial Cysts.—

Anaplasia is equally uncommon in our material. We have seen only six cases in which changes characteristic of anaplasia can be distinguished from degenerative changes due to pressure of hemorrhage within the cyst cavity and within the cyst wall. As in the case of papillary projections, careful original search might discover a greater frequency of anaplasia.

Pseudomucinous Cystoma Arising in an Endometrial Cyst.—

The following case demonstrates an actual neoplasm developing within an endometrial cyst in one ovary together with anaplasia within an endometrial cyst in the other ovary.

The patient, Mrs. E. L. B., FHW No. 585, was a 36-year-old white woman whose previous health had been good. Her menstruation had been entirely normal. She had never been pregnant. For two years prior to admission she had experienced increasing dysmenorrhea, some intermenstrual spotting, occasional menometrorrhagia, and recurrent attacks of severe lower abdominal pain.

Pelvic examination on admission revealed an apparently retroverted, normal-sized uterus and a 6-cm. mass arising to the right of the cervix. At operation the uterus was found to be normal in size and position with numerous endometriotic areas over the anterior surface. A mass about 5 cm. in diameter involved the left adnexa and was intimately adherent to the posterior surface of the uterus. A similar smaller mass was found on the right. Operation consisted of total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy. Her postoperative course was essentially uneventful and she was discharged on the twentieth day. She was alive and well when last seen three years later.

Pathological Findings (Path. No. 29718).—

Gross: The specimen consisted of a complete uterus with attached tubes and right ovary. The left ovary was separate. The right tube and ovary were bound together. The ovary, which had been torn in removal, measured 4 by 3 by 3 cm. and contained an intact 2 cm. cyst filled with clear fluid and a torn 2 cm. cyst which had apparently contained old blood. The left ovary was composed of a previously opened cyst measuring 5 by 6 cm. and containing tarry material. The wall of the cyst was fibrous and was lined with a whitish brown membrane.

Microscopic: Sections from the cyst of the left ovary showed typical endometrial stroma and epithelium which shaded off into areas of larger pale cells with large pale nuclei containing discrete granular chromatin, overlying endometrium-like stroma (Fig. 1). In the cyst wall occasional groups of hemosiderin-laden macrophages were seen. The intact "cyst" in the right ovary was a maturing follicle. The other cyst had a typical endometrial-tissue lining (Fig. 2) definitely connected to a papillary formation with a loose edematous and vascular stroma covered by a multilayered epithelium composed of pale mucus-secreting cells with small discrete and pale nuclei (Fig. 3).

Diagnosis: Late proliferative endometrium; pelvic endometriosis; bilateral ovarian endometriosis and endometrial cysts; papillary pseudomucinous cystoma arising in endometrial cyst of right ovary; bilateral perisalpingitis; periappendicitis.

The question already raised as to whether the pseudomucinous areas occurring in certain endometrial cysts arise originally from germinal epithelium or later from metaplasia of the endometrial epithelium applies to this case. Whatever its exact histogenesis, however, there is no doubt that the papillary pseudomucinous area in the right ovary developed in intimate relationship to the en-
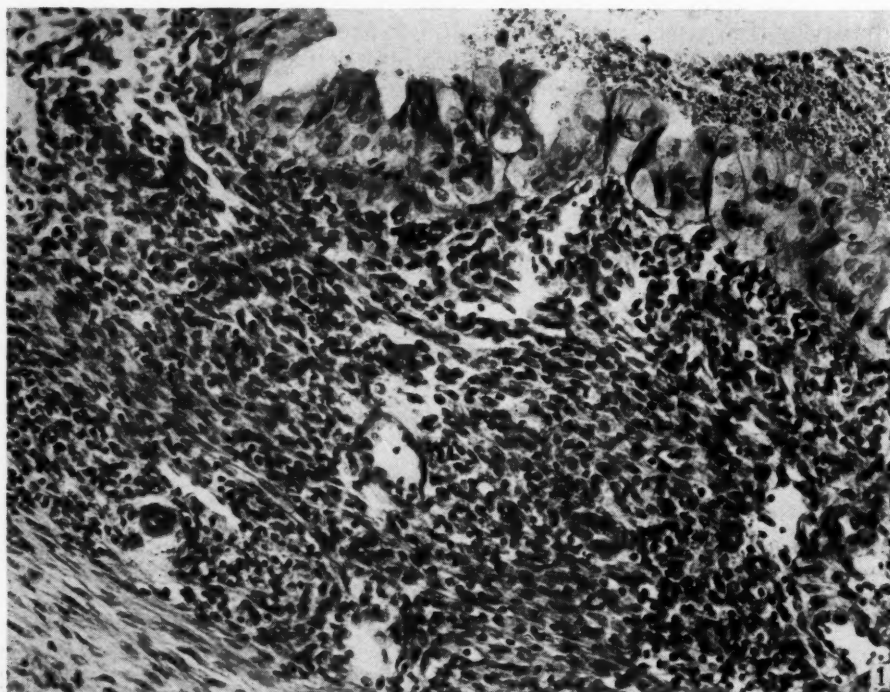
Fig. 1.

Fig. 2.

Fig. 1.—Pathology No. 29718: Photomicrograph of left ovarian cyst showing typical endometrial stroma supporting a multilayered anaplastic epithelium. (×360.)

Fig. 2.—Pathology No. 29718: Photomicrograph of right ovarian cyst showing typical endometriosis on the left and on the right a few anaplastic cells and a papilla of endometriotic tissue. (×200.)

dometriosis.   In the left ovary direct anaplastic transformation of endometrial epithelium apparently occurred.   Further, it is easy to believe that if these lesions had not been interfered with and had become malignant, their origin would have been probably completely obscured.
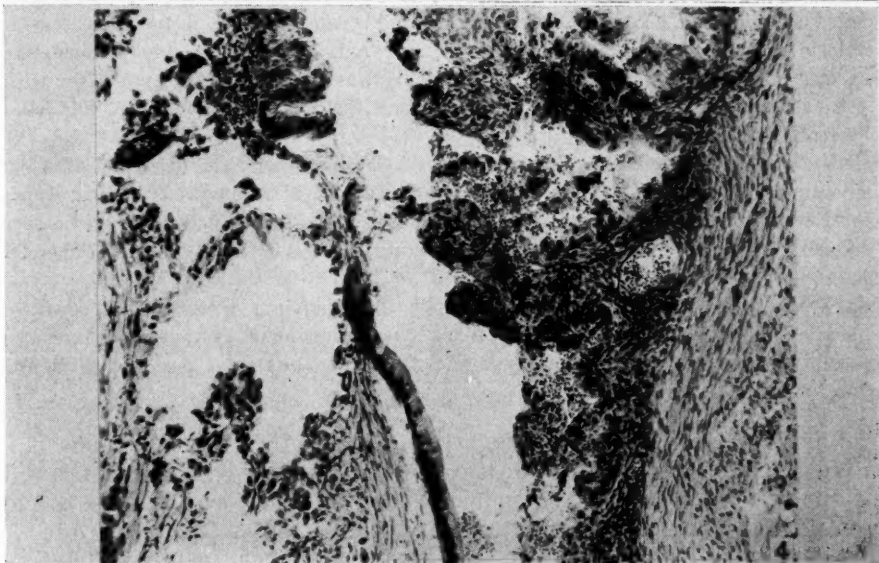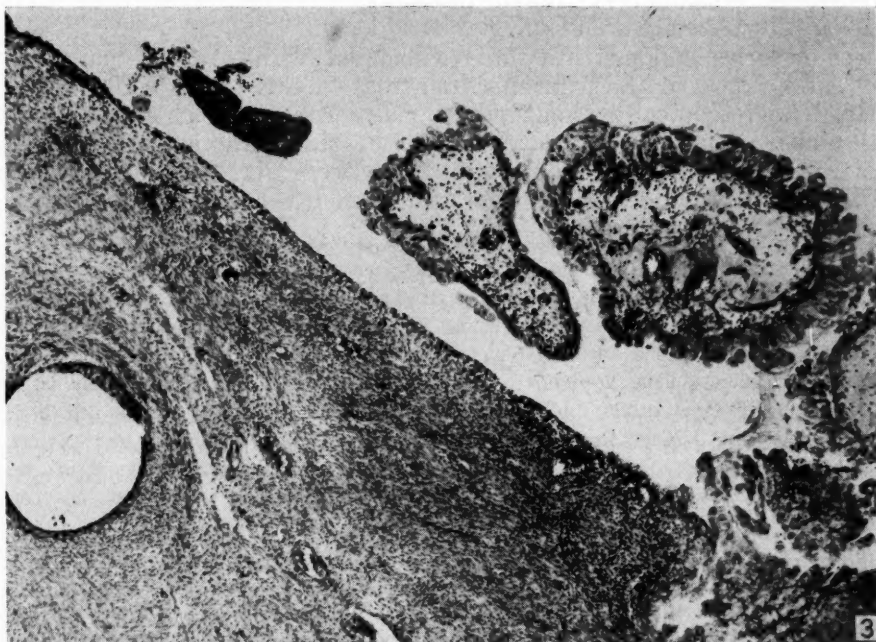
Fig. 3.

Fig. 4.

Fig. 3.—Pathology No. 29718: Photomicrograph of right ovarian cyst showing an area adjacent to that in Fig. 2 with a papillary projection of pseudomucinous type. (×60.)

Fig. 4.—Case 1: Photomicrograph of left ovarian cyst showing pseudomucinous cyst-adenocarcinoma on the left and mucus-secreting epithelium and hemosiderin-laden macrophages in the stroma on the right. (×100.)

Carcinoma Arising in Endometrial Cysts.—

The difficulties inherent in determining the histogenesis of ovarian carcinoma are many. The major ones germane to the present study are the usually widespread nature of the lesion when it first comes to attention, and the striking microscopic resemblance of many ovarian carcinomas to certain endometrial carcinomas. It is, then, not safe to assume an origin in endometriotic tissue merely because endometriosis is also present in the ovary or because the tumor morphologically resembles endometrial carcinoma.

In our series endometriosis was associated with ovarian malignancy in sixteen cases. Two of the ovarian carcinomas in this group could not be distinguished microscopically from endometrial carcinoma. There were in addition a number of carcinomas among the 265 ovarian malignancies that belonged in this category. On the other hand, there were six cases in our series in which an origin in endometriosis appeared possible.

CASE 1.—The patient, Miss M. C., FHW No. 18248, was a 55-year-old white woman whose menstruation had always been normal from menarche at 18 to menopause at 45 years of age. She had had some vaginal staining six years prior to admission. When first seen she had had vague pain in the lower back and right lower quadrant for some time, and had been aware of a mass in the lower abdomen for some weeks.

Upon admission a firm, nontender, irregular mass was noted rising nearly to the umbilicus. The hymen was intact, but on rectal examination a mass could be felt in the culde-sac. At operation a large tense mass adherent to the uterus, sigmoid, and parietal peritoneum was encountered. In freeing the mass it was broken into with release of chocolate-colored fluid. The mass was removed along with the supracervical portion of the uterus and both tubes and ovaries. Her postoperative course was uneventful and she was discharged on the eighteenth day. In spite of therapy with colloidal lead and x-ray, she went steadily downhill and died of carcinomatosis five months later.

Pathological Findings (Path. No. 15982).—

Gross: The specimen consisted of a supracervically amputated uterus with both tubes and ovaries attached. The right ovary was atrophic and contained no gross evidence of endometriosis or carcinoma. The left tube disappeared into a mass chiefly consisting of a collapsed cyst measuring 11 cm. in diameter. This was a multilocular cyst filled with dirty brown grumous material. The walls varied in thickness from 0.5 to 1.5 cm. and the lining was very irregular and friable.

Microscopic: Sections of the left ovarian cyst showed chiefly the existence of a papillary pseudomucinous cystadenocarcinoma invading the wall. In other areas a few typical endometriotic areas were seen. In one section (Fig. 4) an area of transition could be seen from a tall columnar mucus-secreting epithelium overlying a loose stroma containing hemosiderin-laden macrophages to an area of tumor cells.

Diagnosis: Leiomyoma of uterus; atrophic endometrium with residual cystic hyperplasia; senile right tube and ovary; papillary pseudomucinous cystadenocarcinoma of left ovary possibly arising in endometrial cyst of left ovary; bilaterial perioophoritis and perisalpingitis.

The evidence in this case is suggestive, but whether the carcinoma is invading an endometrial cyst or arose in it cannot be established. Nor is the relationship of the two tissues clearly demonstrated. In other words, only the first of Sampson's three criteria is absolutely satisfied. At best this is a probable case of carcinoma arising in an endometrial cyst. However, in our estimation, two types of derivatives of germinal epithelium have occurred within close proximity in the same ovary.

CASE 2.—The patient, Mrs. M. A. H., FHW No. 3503, was a 60-year-old white woman whose menstruation had been perfectly normal from menarche at 15 to menopause at 54 years of age. She had had two pregnancies. When first seen she had had vaginal bleeding

for two years at a rate requiring two pads a day. Four months previously she had had a profuse hemorrhage and had been treated elsewhere with 2,400 mg. hr. of radium for "malignant adenoma" of the cervix proved by biopsy and curettage.

On admission to the hospital examination revealed a firm cervix with a mass of grapefruit size occupying the pelvis. At operation curettage demonstrated a large uterus containing considerable necrotic tissue. On opening the abdomen, the right ovary consisted of an adherent grapefruit-sized cyst which ruptured during removal. There was a smaller cyst in the left adnexal region. Operation consisted of total hysterectomy and bilateral salpingo-oophorectomy. The postoperative course was uneventful and she was discharged on the twelfth day. The patient was followed carefully, without radiation, and never showed evidence of recurrence. She died of a heart attack at the age of 70, ten and one-half years after operation.

Pathological Findings (Path. No. 19118).—

Gross: The specimen consisted of a complete uterus and both tubes and ovaries separate. The uterine cavity was filled by a soft, friable polypoid mass. Although the tumor had invaded the myometrium, it had not yet reached the serosal surface. The right tube was adherent to the ovary which contained a 10 cm. cyst filled with brownish fluid and lined by a yellowish membrane with numerous papillary excrescences. The left tube and ovary were adherent, and the ovary contained a 12 cm. cyst filled with clear fluid.

Microscopic: The uterine tumor (Fig. 5) consisted of glandular polypoid cords, the epithelium of which was composed of multilayered pale cells with discrete large pale nuclei. In some areas the nuclei were more regular and darker staining. One tube contained some fragments of tumor free in the lumen. This had the appearance of an artefact. The right ovarian cyst showed papillary projections arising from a single-layered epithelium in which the nuclei were dark and large (Fig. 6). The underlying stroma was endometrial in appearance and contained hemosiderin-laden macrophages. The epithelium of the papillary projections varied from cells with densely staining nuclei occupying most of the cell to cells with pale cytoplasms and small pale discrete nuclei. In a few areas the tumor was found deep in the wall of the cyst, but nowhere could it be demonstrated in lymphatics.

Diagnosis: Chronic cervicitis; adenocarcinoma of endometrium; bilateral chronic salpingitis; simple cyst of left ovary; papillary adenocarcinoma arising in endometrial cyst of the right ovary.

In this case all of Sampson's criteria are met provided it is considered that we are dealing with two carcinomas arising independently in endometrial tissue. On the other hand, the presence of tumor tissue free in the Fallopian tube may indicate the ovarian carcinoma arose from an implant disseminated from the uterus. If this is the case, it is unusual that there were no other implants in the pelvis and that the patient survived without additional therapy. Although we believe this to be a case of carcinoma arising in endometriosis, we have classified it as only probable because of the uncertainties mentioned above.

CASE 3.—The patient, Mrs. E. McI., FHW No. 34643, was a 55-year-old white woman whose menstruation had always been normal from onset to menopause at 46 years. She had never been pregnant. The right ovary and appendix had been removed when she was 25 years old. For two years prior to admission she had had vaginal staining and pelvic discomfort. Six months before admission she had begun to have increased lower abdominal pain and abdominal distention. Two months prior to admission an exploratory laparotomy elsewhere revealed "inoperable ovarian carcinoma" and she had been treated with 6,500 r of deep x-radiation.

Upon admission a mass was felt in the left lower quadrant rising to the umbilicus. On pelvic examination masses were felt in both vaginal vaults. At operation considerable edema from the previous radiation was encountered. The uterus was small and completely buried in adhesions which involved a large mass in the left adnexa. The pelvis was studded with metastases and the omentum was also filled with them. Except for adhesions and roughening of the surface of the liver the rest of the abdomen was clear. The uterus and
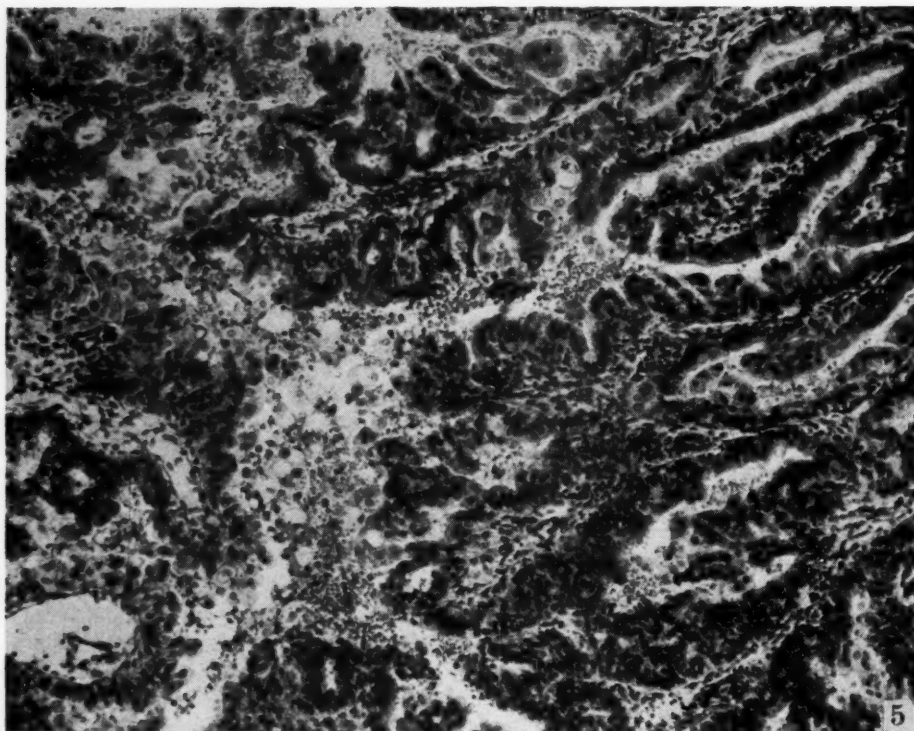
Fig. 5.

Fig. 6.

Fig. 5.—Case 2: Photomicrograph of uterus showing adenocarcinoma of the endometrium. (×100.)

Fig. 6.—Case 2: Photomicrograph of right ovarian cyst showing a transition from endometrium-like tissue on the right to adenocarcinoma on the left. (×75.)
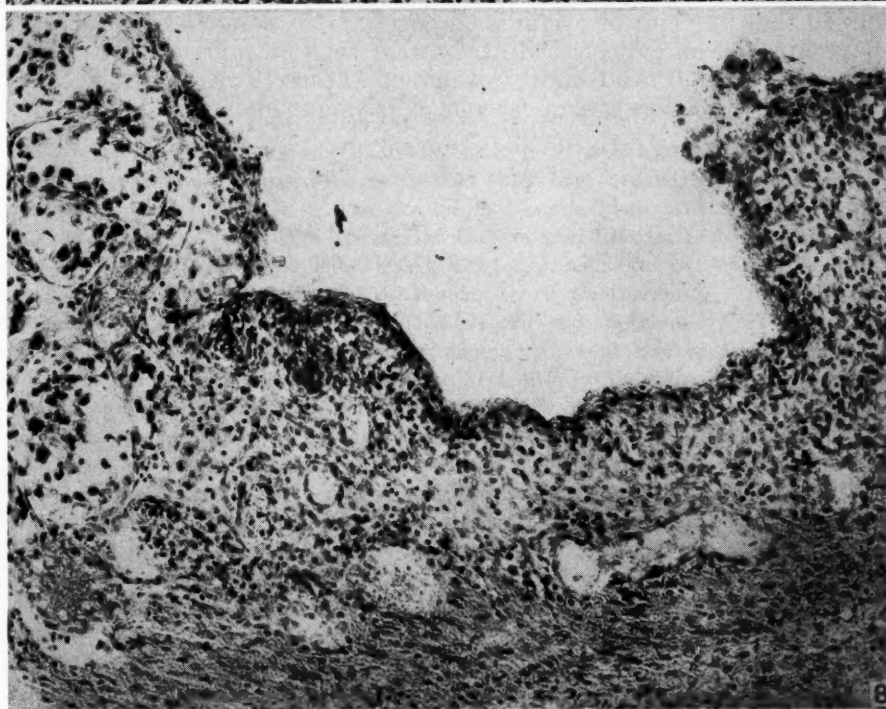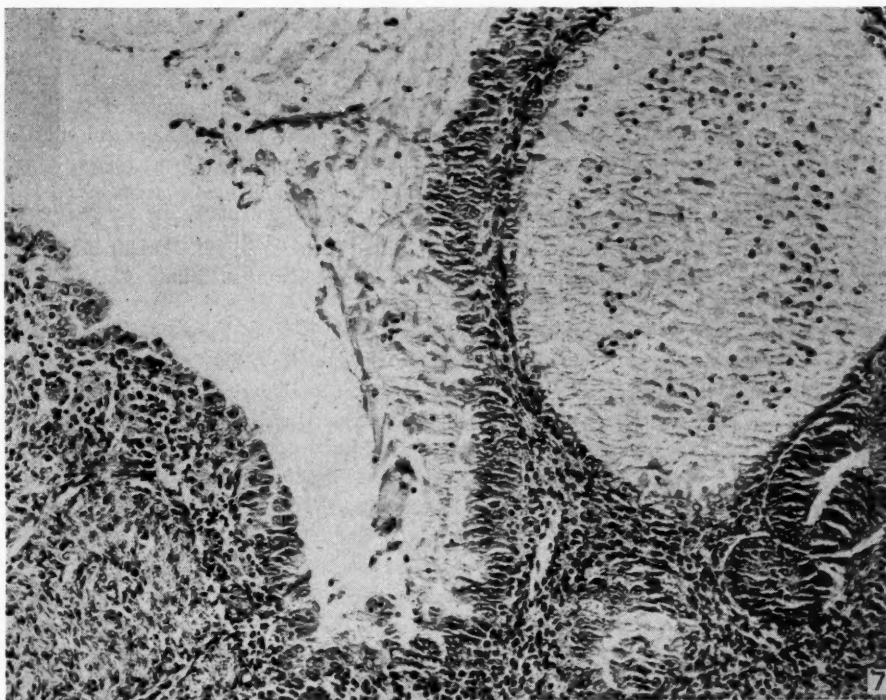
Fig. 7.

Fig. 8.

Fig. 7.—Case 3: Photomicrograph of left ovary showing adenocarcinoma of the ovary with endometrium-like stroma containing hemosiderin-laden macrophages. (×200).

Fig. 8.—Case 4: Photomicrograph of right ovarian cyst showing an area of transition from endometrium-like stroma with degenerated epithelium on the right to adenocarcinoma on the left. (×200.)

left adnexa, and the omentum were removed. The patient withstood operation well and was discharged on the twentieth day. During the remainder of her life she was treated with paracenteses, blood transfusions, stilbestrol and testosterone. She died of carcinomatosis four months after operation.

Pathological Findings (Path. No. S-47-3725).—

Gross: The material received consisted of omentum, and eight pieces of tissue varying from 1 by 1 cm. to 8 by 3 by 2 cm. The omentum was firm and nodular and mottled red-blue and yellow in color. On cut section it was chiefly composed of firm, rough, gray tissue streaked with yellow and containing many hemorrhagic areas and cystic areas filled with thin red fluid. The other pieces of tissue were of similar color and appeared to consist of portions of cyst wall. Two of them contained cysts filled with sticky, brownish, black material. All gave the appearance of being ovarian tissue. No tissue resembling Fallopian tube or uterus was received.

Microscopic: The sections of omentum showed extensive papillary adenocarcinoma. The papillae possessed thin cords of stroma lined by usually stratified epithelial cells. These cells were pale and the nuclei were elongated, to oval and irregular, and were pale and variable in size. Mitoses were fairly common. Two sections of ovary showed two cystic spaces. One of them was a typical endometrial cyst lined with pale regular epithelial cells supported by a thin stroma of small cells infiltrated with hemosiderin-laden macrophages. The other contained a few papillae and a few glands. The epithelium resembled that seen in the sections of omentum. The stroma was thin and endometrial in type and contained many hemosiderin-laden macrophages (Fig. 7).

Diagnosis: Papillary adenocarcinoma of the ovary probably arising in an endometrial cyst of the ovary.

The evidence in this case is quite strongly suggestive, except that no transition from endometriosis to tumor can be demonstrated, and the tumor is so widespread that its point of origin is obscured. It is possible that the carcinoma may have invaded an endometrial cyst rather than have arisen in it. However, Dr. Gunnar Teilum,[13] who kindly examined the sections, agrees with us that this represents a probable case of carcinoma arising in endometriosis.

CASE 4.—The patient, Mrs. A. P., FHW No. 2151, was a 54-year-old white woman whose menstruation had been normal until menopause at age 52 years. She had never been pregnant. For some time she had noticed the presence of a large lower abdominal tumor which had increased in size until it interfered with breathing.

Upon admission the abdomen was greatly distended with fluid, but a mass could be felt in the midline. At operation a large amount of free fluid was encountered. The uterus was small and free. A large cyst extended from the right adnexa to well above the umbilicus. Attached to this cyst was a smaller cyst. The left adnexa also contained a small cyst. The cysts were all ruptured in removal and chocolate-brownish material came from the left ovarian cyst. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. Her postoperative course was uneventful and she was discharged in good condition. She died of carcinomatosis eighteen months after operation.

Pathological Findings (Path. No. 15668).—

Gross: The specimen received consisted of a supracervically amputated uterus with attached left adnexa and the right adnexa separate. The left ovary consisted of a 7 cm. cyst without papillary excrescences and containing grayish brown material. The right ovary was chiefly composed of a dermoid cyst containing bone, hair, and cheesy material. The dermoid was attached by a pedicle 90 cm. in diameter to an 8 by 3 by 3 cm. ruptured cyst containing brownish fluid and many papillary projections. There was a separate cyst on its surface 0.5 cm. in diameter also containing brownish fluid. Section of the pedicle showed a friable papillary growth which had not yet reached the wall of the dermoid cyst.

Microscopic: The left ovarian cyst had a thick fibrous wall with a few hemosiderin-laden macrophages, but no epithelium. The dermoid cyst on the right ovary showed the usual epithelial elements. The small cyst of the right ovary was of endometrial type and other similar cysts were seen in other sections.

The papillary cyst showed areas of typical endometriosis not associated with papillae. The papillae and the cyst pedicle both contained glands filled with pale, highly anaplastic cells with nuclei quite variable in size and staining reaction. Between the papillae were occasional areas lined with mostly absent pale epithelium supported by a cellular stroma quite like that seen in the endometrium (Fig. 8).

Diagnosis: Atrophic endometrium; endometrial polyps with cystic hyperplasia; bilateral chronic salpingitis; endometrial cyst of left ovary; dermoid cyst of right ovary; endometrial cysts of right ovary; papillary adenocarcinoma of right ovary arising in an endometrial cyst.

In spite of the number of different pathological lesions in the right ovary, there can be no doubt as to the origin of the carcinoma in the endometriosis. The areas of transition from endometriosis to carcinoma are not as clear-cut as one could wish, but the existence of endometriosis and carcinoma in different parts of the same cyst is incontrovertible. There is moreover no carcinoma to be found unrelated to the cyst.

CASE 5.—The patient, Mrs. C. L. McC., FHW No. 2392, was a 50-year-old white woman whose menstruation had been perfectly normal until menopause at age 49 years. She had had one pregnancy. She had had symptoms of pressure and bulging in the vagina for about ten months, associated with urgency, frequency, nocturia, and dysuria for six months. She had had occasional vaginal spotting for six months and an occasionally blood-tinged watery discharge for three months.

Upon admission a mass filled the entire pelvis and rose above the umbilicus. At operation the abdomen was opened after biopsy of the cervix, excision of a cervical polyp, cauterization of the cervix, and curettage had been performed. The pelvic organs were found to be matted together with adhesions. The uterus was small. Both tubes and ovaries were involved in large multilocular masses. Operation consisted of supracervical hysterectomy and bilateral salpingo-oophorectomy. The patient's postoperative course was uneventful and she was discharged on the twenty-first day. She subsequently received 3,200 r of x-radiation. She was alive but suffering from multiple sclerosis when last heard from six years later.

Pathological Findings (Path. No. 23129).—

Gross: The specimen received consisted of a cervical polyp, a cervical biopsy, and a small uterus with attached bilateral tuboovarian masses. The left tuboovarian mass measured 8 cm. in diameter and contained several follicle cysts, and two larger cysts one of which had papillary excrescences both on the surface and in its cavity. The other was smooth walled and contained brownish mucoid material. The right tuboovarian mass measured 6 cm. in diameter and contained several cysts filled with brownish material. There were papillary growths on the surface and within the ovary.

Microscopic: The papillary areas in both ovaries showed chiefly a thin to dense regular stroma supporting an often multilayered epithelium with considerable variation in size and shape of nuclei. Frequent areas of squamous metaplasia were seen (Fig. 9). In the left ovary several typical areas of endometriosis were seen, including some areas within the tumor-containing cyst which blended into carcinoma (Fig. 10).

Diagnosis: Chronic cervicitis; endometrial polyp of cervix; atrophic endometrium; bilateral chronic salpingitis; adenoacanthoma of ovaries arising in an endometrial cyst of the left ovary.

In this case adenoacanthoma appears to have arisen within an endometrial cyst in one ovary and to have broken through the cyst wall and spread to the other ovary.

CASE 6.—The patient, Mrs. M. C., FHW No. 31706, was a 54-year-old white woman whose menstruation had been normal from menarche at 13 to menopause at 46 years of age. She had had one pregnancy. A month prior to admission she had had acute urinary retention requiring catheterization, and since that time had been able to void only lying down. For two months her abdomen had seemed bloated.

Upon admission an irregular mass rose from the pelvis almost to the umbilicus. At operation the omentum was adherent to the pelvic viscera. The uterus was small. The

right ovary was replaced by an irregular mass and fleshy cystic tissue was cut through in removing the mass. The left tube and ovary were bound together. The right ovarian mass and a portion of the tube were removed together with the left tube and ovary. The patient's postoperative course was uneventful and she was discharged on the tenth day. She subsequently received 3,100 r of supervoltage x-radiation and she was alive and well without evidence of recurrence eighteen months later.
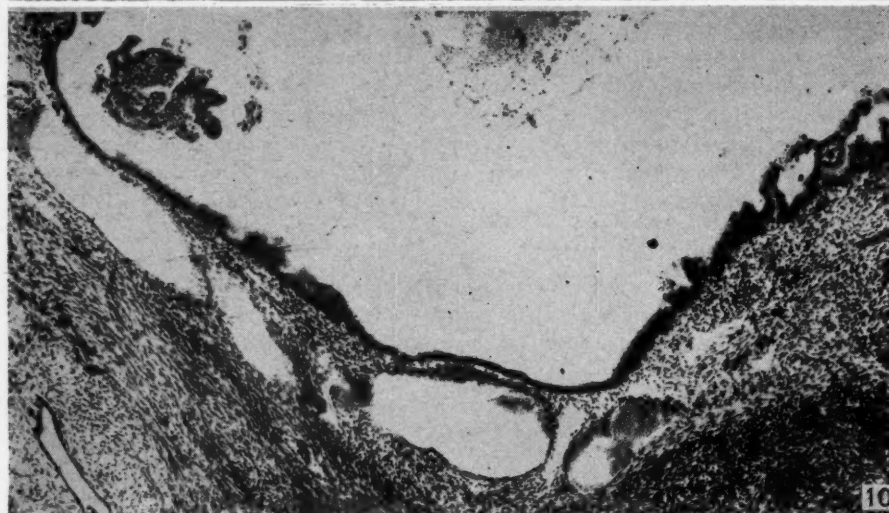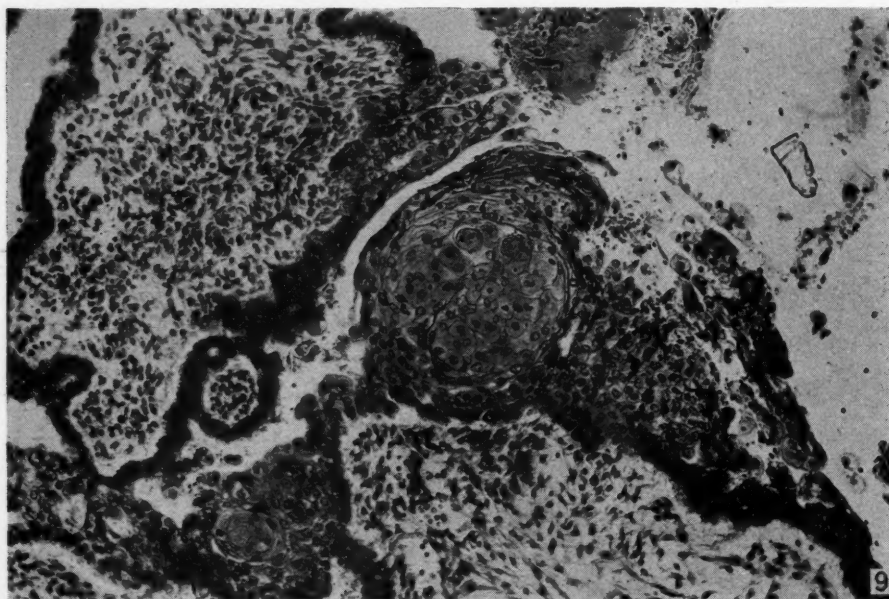
Fig. 9.

Fig. 10.

Fig. 9.—Case 5: Photomicrograph of left ovary showing nests of squamous epithelium in an adenoacanthoma. (×200.)

Fig. 10.—Case 5: Photomicrograph of left ovary showing an area of endometriosis in the same cyst. (×90.)

Pathological Findings (Path. No. S-46-4261).—

Gross: The specimen consisted of the left tube and portions of the left ovary, the right ovary, and a portion of the right tube. The right ovary measured 15 by 7 cm. and con-

tained an 11 by 5 cm. cyst filled with brownish fluid. Its wall had many friable papillary projections which were pale brown in color. The pedicle of the ovary contained friable, soft fleshy tissue.

Microscopic: The right ovary showed numerous cystic areas surrounded by typical fibrous ovarian tissue and lined by variable epithelium usually columnar and having cytoplasmic projections simulating cilia. In other areas it possessed typical cilia and some cells resembling tubal epithelium. The papillary portions of the cyst showed numerous papillae with multilayered epithelium which was quite variable in size and shape of cells and in the staining characteristics of the nuclei. In many places invasion of the stroma was taking place. In one area (Fig. 11) the wall of the cyst consisted of a thick layer of endometrial-type stroma filled with hemosiderin-laden macrophages. The epithelium was chiefly lost from this area but where present was of the endometrial type. In the center of this area was a typical papillary projection of tumor.

Diagnosis: Atrophic left tube and ovary; serous cystadenocarcinoma of the right ovary arising in an endometrial cyst of serous cystadenofibromatous origin.
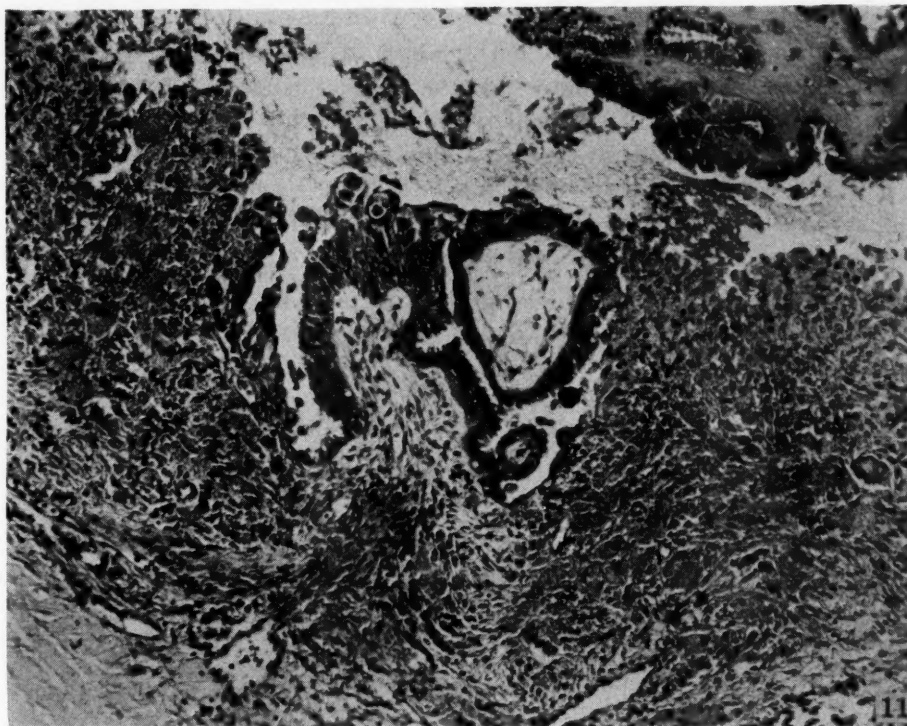

Fig. 11.—Case 6: Photomicrograph of right ovarian cyst showing a papillary area of serous cystadenocarcinoma in the center surrounded by stroma without epithelium consisting largely of hemosiderin-laden macrophages. (×100.)

The intimate relationship of serous cystadenocarcinoma and endometriosis in this case cannot be denied. Whether they arose side by side or whether the tumor arose from a change in the endometriosis cannot be positively stated. It is our belief however that endometriosis developed within one of the cystic spaces within a serous cystadenofibroma and that later a serous cystadenocarcinoma also developed therein.

Summary and Conclusions

Proved cases of ovarian carcinoma arising in endometriosis are exceedingly rare. In a study of 889 cases of ovarian endometriosis and 265 ovarian malig-

nancies occurring in a forty-five year period at The Free Hospital for Women, we have found three undoubted cases of this type to add to the eight cases previously reported in the literature. In addition we have found three highly probable cases.

The probable precursors of carcinoma arising in endometriosis are also rare. We have seen true papillary projections in only five endometrial cysts and anaplasia only six times. In one case we found a benign neoplasm, a pseudomucinous cystoma, arising in an endometrial cyst.

In the course of our study we encountered nine cases which strongly support the celomic metaplasia theory of the origin of endometriosis. These cases in which endometriosis arose from germinal epithelial elements also strongly suggest that serous and even pseudomucinous cysts arise from ovarian germinal epithelium.

It is our feeling that carcinoma may arise in association with endometriosis by two means. The first, exemplified by cases in which mixed types of epithelium are found, is by malignant changes in the nonendometrial portions of these mixed cysts. Examples seen by us include the benign pseudomucinous cystoma, a pseudomucinous cystadenocarcinoma probably arising in an endometrial cyst, and a serous cystadenocarcinoma definitely arising in close proximity to endometriosis. The second is by malignant transformation of endometriosis as in one probable and one definite case of papillary adenocarcinoma and one definite case of adenoacanthoma of this origin.

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THE EFFECT OF ADRENALIN ON THE PREGNANT HUMAN UTERUS*

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A N UNDERSTANDING of the effect of Adrenalin on the pregnant human uterus is important for the following reasons:

1. Adrenalin has frequently been suggested for specific therapeutic use in pregnant women, especially during labor.

2. Adrenalin is commonly mixed with the local anesthetic agents used for nerve-conduction blocks during labor or delivery.

3. Adrenalin simulates in many ways the action of the sympathetic nervous system, which participates in the innervation of the uterus.

4. Adrenalin plays a part in the body's adaptation responses. This adaptation is particularly significant in times of emotional stress such as is occasioned by painful labor.

Various contrary effects of adrenalin on the pregnant human uterus in situ have been described in the literature. It has been said to diminish contractions, to increase them, to increase and then diminish them, and to diminish or increase them according to dose.

A critical re-evaluation of the work on Adrenalin appears to be in order. The following study, in which the Reynolds multiple-channel tokodynamometer (TKD)[14, 15] has been employed, constitutes a repetition by a new technique of the experimental work already done and an extension into new directions. The use of the TKD has simplified the study of uterine contractions and introduced a method which is safer for the patients than the customary intrauterine balloon. In addition, the TKD demonstrates the different patterns of coordination of uterine activity.

Materials and Methods

The patients studied in this report were chosen from the clinic populations of the Sinai and Johns Hopkins hospitals. The outpatients studied, when not in labor, returned home after the conclusion of a two-hour period of recording. All patients subsequently delivered in one of the two hospitals. No deleterious effects from the administration of the test substances were observed in mothers or infants.

Recordings of uterine activity were made with the Reynolds multichannel tokodynamometer. The TKD is an externally placed device having pickups which rest directly on the abdomen. The changes in uterine pressure against these pickups are converted into electrical energy by strain gages and then recorded. Recordings were made either by a spark-tape recorder or by pen-motors after amplification of the direct current impulses.

The curves observed were similar to those obtained by others with either the Lorand tocograph or intrauterine bags or balloons. However, the TKD, in contrast to intrauterine bags and balloons, does not induce uterine activity. Further, its multiple leads provide simultaneous recordings from several areas of the anterior wall of the uterus, thereby depicting the whole uterine contraction pattern and not simply the activity of one area.

Adrenalin was used as Adrenalin Chloride 1:1,000 and administered by hypodermic syringe. For intravenous drip, this drug was diluted in either normal saline or 5 per cent glucose solution and given in standard intravenous drip apparatuses with a calibrated rate of flow. In each type of experiment, controls with either glucose or saline solution alone were employed. The obstetrical posterior pituitary extract, Pituitrin, was given by hypodermic syringe.

Results

The effect of Adrenalin upon the activity of the pregnant human uterus depends upon the concentration of the drug at the effector organ or organs. In high concentration, Adrenalin induces uterine contraction. This concentration cannot be maintained because of its profound systemic effects. In low concentration, so low in fact as to have no other clinically demonstrable action, Adrenalin is strikingly inhibitory to uterine activity. The sudden withdrawal of even these minute amounts of Adrenalin is followed by an increase in uterine activity.

For clarity of presentation, the effect of administration of Adrenalin will be described as it is manifest upon the pregnant uterus in labor and the pregnant uterus during pregnancy but not yet in labor, with or without spontaneous uterine activity.

I. *Pregnant, Not in Labor.*—

These records were two hours in length, with control periods of forty to sixty minutes.

a. *Little or no uterine activity in the control period.*—When 0.6 mg. (10 minims) of Adrenalin is given intravenously in from thirty to sixty seconds, an almost immediate oxytocic effect is noted throughout the uterus as demonstrated by the multiple leads of the TKD. This often begins before the injection is completed. In the earlier weeks of the last trimester, when there is usually little uterine activity, the actual force of these induced contractions is small, but as the patients near term it becomes greater. There may be a single contraction or a series of contractions. When a single contraction occurs, it is noticeable that the rise and fall are more rapid than is observed in spontaneous contractions. The peak is usually reached within twenty seconds of the onset of the contraction and the force promptly drops off. Before this first contraction can fall to the previous base line a second weaker contraction may supervene. In a few records as many as four weaker contractions were observed. Once these are over no further uterine activity is seen. The systemic effects are quite marked at this dosage level in every patient, but occasionally the oxytocic effect may be absent.

Intramuscularly administered Adrenalin in amounts ranging from 0.2 to 0.5 mg. (3 to 7 minims) has no demonstrable effect on uterine activity in these patients.

b. *Moderate to marked spontaneous uterine activity.*—Adrenalin administered intravenously to these patients in amounts similar to those given to the previous group produces similar contractions of the uterus followed by a period of inhibition.

Intramuscularly administered Adrenalin in amounts between 0.2 and 0.5 mg. (3 to 7 minims) inhibits uterine activity in the great majority of patients.

This inhibition may be observed in the complete absence of systemic effects. It usually appears within five minutes of the administration of the drug and is maximal for the following ten minutes. It then wanes and in about twenty-five minutes is absent. The other characteristics of this inhibition may be outlined as follows:

1. Diminution in the force of uterine contractions throughout the uterus. There may be complete disappearance of contractions.

2. Increase and inequality in the length of the interval between contractions. This is not seen as clearly here as it is in the patients in labor described below, but in those patients who manifest a high order of rhythmic activity it may be detected.

3. Decrease in uterine tone during the peak of Adrenalin effect.

c. *Induced uterine activity.*—A number of patients who exhibited little or no spontaneous uterine activity were given Pituitrin intramuscularly in 1 minim doses. They were also given Adrenalin either before or after the Pituitrin. In either event, the Adrenalin usually caused a diminution of the expected oxytocic effect of the Pituitrin.

II. *Pregnant, in Labor.—*

The administration of Adrenalin intramuscularly in amounts between 0.2 and 0.5 mg. (3 to 7 minims) to patients in active labor results in inhibition in most instances. This inhibition is the same in all respects as that observed in patients not in labor except that the higher order of uterine activity in patients in labor makes the inhibition more striking. These effects are clearly demonstrated in Figs. 1 and 2. There appears to be a rough relation between the degree of uterine activity and the amount of Adrenalin required to produce inhibition. It is also notable in this group that inhibition may be present in the absence of systemic effects and vice versa.

Inhibition by intramuscularly administered adrenalin has been observed in patients under systemic sedation and caudal analgesia as well as in those who were receiving no analgesia of any kind.

The administration of Adrenalin by dilute intravenous drip, so that minute amounts of Adrenalin are placed in the circulation in an arm vein, results in fundamentally the same type of inhibition as intramuscular administration. There are however, important differences, and for this reason, detailed description of the experimental situation is warranted.

These patients were observed either under systemic sedation, or in the presence of conduction blocks by the continuous caudal technique, or without any analgesia at all. They were all cooperative patients who were obstetrically normal and who could be expected to deliver with rapidity. The intravenous drug was administered as if it were part of the regime of care during labor and every precaution was taken to avoid suggesting any effect to the patient. In some instances two bottles, one containing the Adrenalin and the other a saline or glucose control solution, were connected to a three-way stopcock and the solutions interchanged at will. No Adrenalin was mixed with the anesthetic agents used for caudal blocks.

Prior to venipuncture the drip sets were adjusted to deliver the solution at 2 c.c. per minute, a dose of Adrenalin of 0.05 mg. (less than 1 minim) every twenty minutes, or 2.5 micrograms (less than 0.05 minim) every minute. This adjustment prevented a large dose from entering the circulation suddenly as it might if the drip were instituted before its rate of flow was regulated. This dose was found to be effectual, and the volume of solution of such magnitude that the dose could be quadrupled without danger of imposing an excessive load upon the patient's circulation.

If there were no loss of Adrenalin from the circulation either by diffusion or destruction, this dose level of Adrenalin would produce an increment of about 0.1 microgram per cent in the blood Adrenalin level in the first two minutes. It is within this time period that the effect of Adrenalin on uterine contractions can be detected in several of the cases. Further, this dose level does not produce any clinically detectable systemic effects, as judged by pulse rate, blood pressure, and peripheral vascular tone.
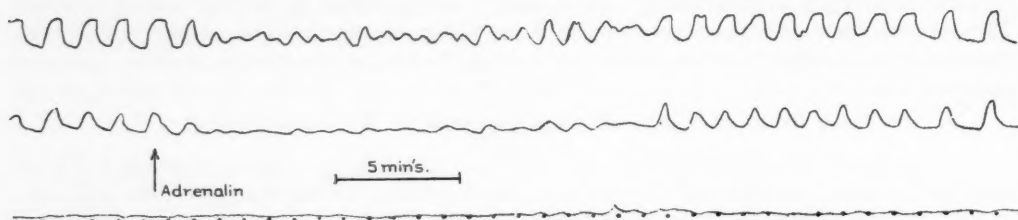

Fig. 1.—Intramuscular Adrenalin without analgesia.
    TKG of a para 2-2-0-0-2 in labor, at term. Top lead records an area 8 cm. above the umbilicus; middle lead, just below the umbilicus; lower lead 10 cm. below the umbilicus. At the left the cervix was 3 cm. dilated, and at the right 4 cm. dilated. Adrenalin, 0.5 mg. (7 minims) intramuscularly, was given at the arrow. The inhibition and disorganization of uterine activity are demonstrated.
    This record, and that in Fig. 2, were made on the spark-tape TKD at the Johns Hopkins Hospital.
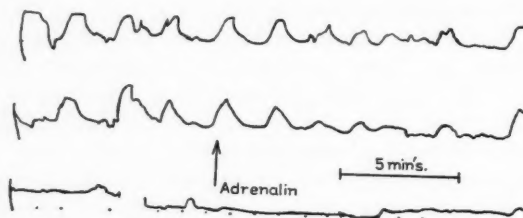

Fig. 2.—Intramuscular Adrenalin without analgesia.
    TKG of a para 3-3-0-0-3 in labor, at term. The leads were placed similarly to the leads in Fig. 1, except that the middle lead was to the right of the mid-line. At the left the patient was 8 cm. dilated, and at the right 10 cm. dilated. Adrenalin, 0.5 mg. (7 minims) intramuscularly, was given at the arrow. The ability of Adrenalin to inhibit uterine activity late in active labor is demonstrated.

In addition to the effects of Adrenalin already described under I, b, the following characteristics of the effect of dilute Adrenalin by intravenous drip were noted:

1. Relative recovery from inhibition during a period of administration at a constant dose level. Inhibition appears within a minute or two after the start of an Adrenalin drip and is usually noticeable in the very first contraction by a decrease in its size in comparison to the previous average. The effect is maximal within three or four minutes and uterine contractions may be absent for several minutes. There is then a gradual recovery from the effect of the Adrenalin until after fifteen minutes the force of contractions has increased to about two-thirds of the previous average. Individual contractions may exceed in force the relatively weaker ones observed prior to the drip. In no case has a patient been observed longer than twenty minutes with a single constant rate of flow and it is not possible to state whether over a longer period of time complete recovery might not take place. The wave shapes of these contractions are usually identical with those prior to the Adrenalin drip once some recovery from inhibition has occurred.

2. Re-establishment of the inhibition when the rate of drip is increased. If, after relative recovery has occurred, the rate of administration is doubled, to 0.1 mg. (1½ minims) every twenty minutes, the previous degree of inhibition is re-established. This period of inhibition in its turn wanes in about the same time period as the initial dose. A third increment is followed by the same phenomena, except that at this dose level, 0.2 mg. (3 minims) every twenty minutes, systemic effects make their appearance in the form of tremulousness and peripheral vasoconstriction. There may also be a slight rise in blood pressure but this is not consistent.
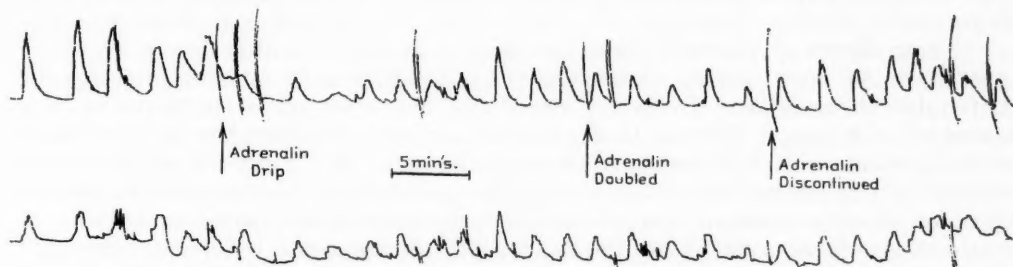

Fig. 3.—Intravenous Adrenalin drip with candal analgesia.

TKG of a para 1-1-0-0-1 in labor, at term. The upper lead records the area in the mid-line 4 cm. above the umbilicus, the lower lead 4 cm. below the umbilicus. At the left the cervix was 5 cm. dilated, and, between the first and second arrows, fully dilated, with the vertex on the perineum. At the right the vertex began to crown. Throughout the period of Adrenalin administration the level of sensory anesthesia was up to T-9.

At the first arrow intravenous drip at a rate of 0.05 mg. every twenty minutes was begun and at the second arrow this was doubled. At the third arrow Adrenalin was discontinued.

In both leads there is decrease in tone and force of contractions immediately following the start of the drip. This decrease wanes but when the rate is doubled another decrease occurs. Following discontinuance of the drip the force of contractions increases and then the "rebound," with a marked increase in tone, follows.

This record and that in Fig. 4 were made on the amplifier-penmotor TKD at Sinai Hospital.
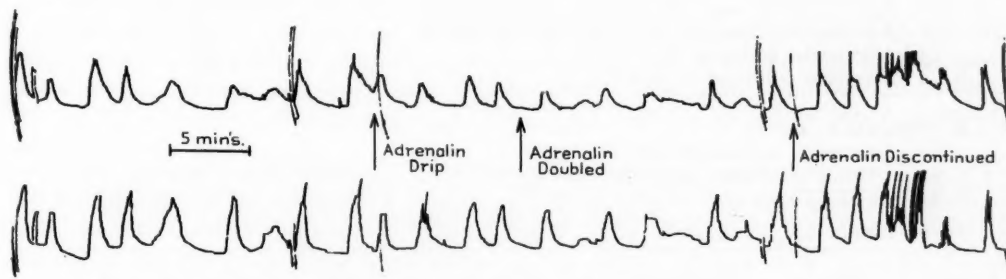

Fig. 4.—Intravenous Adrenalin drip without analgesia.

TKG of a para 1-1-0-0-1 in labor at term. The upper lead records an area in the mid-line about 8 cm. above the umbilicus, while the lower lead is 1 cm. above the umbilicus. Because of differences in amplification, the deflections in the lower lead appear greater than those in the upper. In fact, however, they are not.

At the start of the record the cervix was 3 cm. dilated and at the end 9 cm.

Adrenalin was given as in Fig. 3.

The inhibition following the initial rate of flow is not striking but when the flow is doubled all the features of Adrenalin inhibition appear. The "rebound" phenomenon is marked in the upper lead.

3. Rebound from the inhibition when the drip is discontinued. In each case thus far observed the Adrenalin drip has been abruptly discontinued. Uterine activity returns promptly to the force observed prior to the drip. After five to seven minutes have elapsed, there is a further increase in the force of the uterine contractions and a simultaneous increase in the tone of the uterus, as represented by the base line between contractions. This lasts for about five

contractions and then vanishes. In one case the rise in tone was so great that the force exhibited by uterine tone between contractions exceeded the force of the greatest uterine contraction prior to the drip. If the patient is not under conduction block there is a great increase in discomfort during this rebound from inhibition.

In no case has the withdrawal of the Adrenalin drip been gradual, so that it is not possible to say whether the suddenness of the withdrawal is the crucial factor in this phenomenon. The absence of the rebound phenomenon following intramuscular administration suggests that this is the case. No patient has been observed longer than thirty minutes following withdrawal of the Adrenalin drip.

These effects of Adrenalin drip may be seen in Figs. 3 and 4.

There is no evidence that transitory inhibition of uterine activity by Adrenalin slows labor. However, the deliberate selection of patients in very active labor makes it difficult to decide this matter. The fact that at least some of the patients accomplished considerable dilatation of the cervix while uterine activity was inhibited may indicate that the gradient of force is more important than its absolute amount. Analysis of these records has been carried out to compare the force exerted in the fundus and midsegment before, during, and after inhibition by Adrenalin drip. In general, the force exerted by the fundus exceeded that of the midsegment regardless of Adrenalin inhibition and in no case was there a reversal of this gradient, no matter how profound the inhibition and disorganization of uterine activity. In occasional contractions the midsegment exceeded the fundus but this unfavorable gradient was observed before, during, and after the Adrenalin drip.

TABLE I

TYPE OF EXPERIMENT	NUMBER OF PATIENTS
A. Patients Not in Labor.—	
Undiluted Adrenalin, intravenous	13
Adrenalin 0.2 mg. (3 minims) intramuscular	17
Adrenalin 0.5 mg. (7 minims) intramuscular	17
Adrenalin followed by Pituitrin	39
Pituitrin followed by Adrenalin	35
	121
B. Patients in Labor.—	
Adrenalin, intramuscular	12
Adrenalin, dilute intravenous drip	7
	19
Total	140

Discussion

There have been but few experimental studies reported on the effects of Adrenalin on the pregnant human uterus during the last trimester of pregnancy or in labor. In all of these, uterine contractions were recorded by use of a bag or balloon in the cervix or uterus, attached to a manometer, to comprise a tocograph. The first report was that of Rucker in 1925,[16] who noticed that analgesic sacral blocks, performed with Novocain just before delivery, seemed to diminish uterine contractions in some of his cases, but not in others. Investigation revealed that 5 minims of Adrenalin were mixed with the Novocain in all the cases in which uterine activity was diminished, and only in those cases. This led to a series of experiments, in which uterine contractions were recorded in women just before and during labor. Rucker found that subcutaneous injection of 5 minims of Adrenalin caused diminution of uterine contractions, but that 2 minims caused no change.

Two years later, in England, Bourne and Burn[2] reported the effect of Adrenalin on the uterine activity of two women in labor. One woman was given 5 minims and later 10 minims subcutaneously, while the other received 5 minims intravenously. In each instance they observed inhibition of uterine contractions. Both Rucker and these authors suggested that a practical application of this action of Adrenalin would be to relax the uterus in the event of uterine spasm, or to diminish uterine tone when desired.

The next experimental work on this subject was published in 1938, when Woodbury, Hamilton, and Torpin[26] reported the effects of 0.1 mg. of Adrenalin given intravenously. They found a marked, prompt rise in intrauterine pressure, followed by a fall below normal, and then return to normal. Brown and Wilder[4] agreed with them quite closely, in 1943, when they wrote that intravenous or intramuscular Adrenalin causes prompt contraction of the uterus during labor, with heightening of a contraction that has already started. This is followed by what they call a compensatory pause. They used 1 to 2 minims of Adrenalin. Brown and Wilder reviewed Rucker's and Bourne and Burn's reports, and interpreted Bourne and Burn's one published record (5 minims of Adrenalin intravenously) as showing an immediate contraction followed by diminished activity. Brown[3] classified as "doubtful" what Rucker considered diminution of uterine activity.

Finally, in 1944, Woodbury and Abreu[27] demonstrated that the action of Adrenalin on the uterus is different in different concentrations. They stated, "It is a common pharmacological observation that epinephrine in proper dosage can produce either excitatory and/or inhibitory effects on a number of structures innervated by the sympathetic nervous system." Woodbury and Abreu gave an unspecified number of patients at term from 0.01 to 0.1 mg. of Adrenalin in relatively concentrated to extremely dilute solutions intravenously. Uterine activity had already been induced and recorded by means of an intrauterine balloon on a catheter. They observed that the relatively high concentrations induced uterine contraction followed by diminution of uterine activity, and that the low concentrations produced diminution alone.

As Woodbury and Abreu pointed out, previous investigators had already demonstrated both the excitatory and inhibitory effects of Adrenalin, but until their study no one had employed a sufficiently wide range of doses to produce both effects. The differences among the reports were therefore more apparent than real.

The present study confirms Woodbury and Abreu's observations. The effect of Adrenalin on the pregnant human uterus depends entirely upon its effective concentration at the site of action. This in turn depends upon the size of the dose and the route of administration.

Adrenalin in high concentration is an oxytocic substance throughout the uterus. Its systemic effects are so marked that it is doubtful whether such concentrations ever occur clinically and whether they are safe therapeutically. The contractions induced are different in their wave shape from those of spontaneous activity.

Adrenalin in low concentrations is inhibitory to uterine activity throughout the uterus. In these concentrations there may be no systemic effects at all. The inhibition is characterized by diminution of the force of uterine concentrations without change in the gradient of force in the uterus as a whole, by decrease in uterine tone, and by disturbance of the rhythmicity of contractions.

There have been many references in the clinical literature to the use of Adrenalin for therapeutic purposes in obstetrics.[5, 6, 10, 17, 18, 19, 22, 23, 24, 25] The great majority of these are based upon the concept that Adrenalin diminishes uterine contractions and tone. It has not, however, been sufficiently emphasized that in many of the situations in which Adrenalin has been recommended its

intravenous administration, undiluted, is hazardous. The drug has its rational uses when transitory inhibition of uterine activity is desired. Adrenalin has the significant advantage that, in doses adequate to inhibit the uterus, it has mild or no systemic effects on the mother. The other uterine inhibitors in common clinical use, ether, chloroform, and morphine, are all powerful respiratory depressants for the fetus. This is not true of Adrenalin. In addition, when Adrenalin is given by the route of choice, slow intravenous drip of a very dilute solution, its effect can be halted promptly by cessation of the drip. The principal disadvantage of Adrenalin for clinical use is the brevity of its action. Since the time relationships of this action are relatively constant, they should be considered in the rational employment of the drug. The maximum effects by intravenous drip occur in five minutes and last for another ten minutes, if the rate of flow is not increased.

Adrenalin in combination with local anesthetic agents in nerve-conduction blocks during labor does not significantly affect uterine activity. A commonly used concentration of Adrenalin for this purpose is 1:200,000, or 0.005 mg. of Adrenalin per cubic centimeter.[7] Even the large single dose of local anesthetic employed in pudendal block does not ordinarily exceed 40 c.c. by volume. By the caudal route, the single-dose technique employs volumes of about 30 c.c. and the continuous technique smaller doses. In all of the sites where these doses are given absorption is relatively slow compared to the intramuscular route. The maximum single dose is therefore in the range of 0.2 mg. (3 minims) which is the lower margin of effective dose by the intramuscular route in labor. The smaller amounts administered in any of the continuous conduction-block techniques can be disregarded since they are well below the effective dose range.

Despite what has been said above in reference to local anesthetics, Adrenalin is effective in extremely low concentration. Increments in blood level which cannot exceed 0.1 micrograms per cent produce definite inhibition. Actually, the diffusion and destruction of Adrenalin are so rapid that the increment must be lower by far than this maximum. The best available chemical means for the detection of Adrenalin in the blood are too gross to detect such low concentrations as these.[11] This of course presents a serious obstacle to the study of the influence of endogenous Adrenalin secretion upon uterine activity.

Magnesium ion has been described as an effective uterine spasmolysant.[1] In appropriate doses it will either prevent or halt uterine tetany induced by the administration of oxytocics, such as Pituitrin, Pitocin, ergonovine, Methergine and quinine, to patients not in labor. It does this without abolishing uterine contractions, however. Abarbanel states, "No observable effect (of magnesium) was noted upon the pattern of uterine motility" in labor. In the present study there has been no opportunity to study the effect of Adrenalin upon uterine tetany. Its effect on the uterine activity in other respects appears to be quite different from that of magnesium.

Two features of the response of uterine activity to a dilute intravenous drip of Adrenalin remain to be clarified further. The recovery of uterine activity from inhibition during a constant rate of flow appears to be incomplete. An increase in the rate of flow restores the inhibition. The recovery is not accounted for by an increase in the systemic destruction of adrenalin, since increase in the rate of administration eventually produces systemic effects which persist even while the effect on the uterus is waning. This would appear to localize the recovery mechanism to the site of action of Adrenalin on uterine activity. The rebound phenomenon observed following sudden withdrawal of the drug may represent a "running away" of the mechanism for recovery from inhibition. However, unlike the other responses, it is not observed immediately but after a lag of several minutes. This may indicate the existence of remote compensatory mechanisms as well as the local one.

The way in which Adrenalin exerts its effect upon the uterus is still unclear. The drug is known to be an inhibitor of synaptic transmission in the sympathetic nervous system in low concentration.[8, 9, 12] However, inhibition of uterine activity has been observed in the present study in the presence of an effective caudal nerve-conduction block with a level of sensory anesthesia up to the eighth thoracic segment. This localizes the site of action of Adrenalin to:

1. Motor nerve fibers which may not be completely blocked by this technique.

2. Sensory nerve fibers cephalad to T 9.

3. Sensory nerve fibers peripheral to the site of nerve block whose central connections are below the level of T 8. This, of course, includes the poorly understood intrinsic ganglionic fibers of the uterus itself.

4. The uterine musculature proper.

Study of the uterine response to Adrenalin under more extensive and more profound nerve conduction block than employed here may be expected to localize the site of action further.

The implications of these observations on Adrenalin in the study of dystocia are provocative. In difficult labor there is a state of emotional stress which may well induce excessive secretion of endogenous Adrenalin. The disorganization of patterns of uterine activity observed in inertial labor resembles in many respects that induced, for brief periods, by exogenous Adrenalin. Each contraction in its turn may be inhibited as a result of the very apprehension it induces. It is conceivable that the mechanisms for recovery from inhibition do not come into play because the secretion of Adrenalin is intermittent rather than continuous. Systemic sedation and nerve-conduction blocks may in some cases shorten the length of labor by allaying apprehension and breaking this cycle. It may reasonably be asked why, if this is the case, every excited patient does not suffer inertial labor. Perhaps the answer is that the response to a given dose of Adrenalin differs in different patients. Lines of experimental analysis which suggest themselves are the employment of adrenolytic substances in therapy when and if sufficiently safe compounds become available, and the determination of blood Adrenalin levels during labor, especially in the presence of dystocia.

Summary

The effect of Adrenalin on the activity of the pregnant human uterus has been studied in 140 patients with the Reynolds multichannel tokodynamometer (TKD). One hundred twenty-one of these patients were between the twenty-sixth and fortieth weeks of pregnancy, but not in labor, and nineteen were in labor, at the time of the recording.

The effect of Adrenalin depends entirely upon its concentration at the site of action. In high concentration it is oxytocic throughout the uterus, producing contractions which differ in their pattern from those of spontaneous activity. In low concentration, Adrenalin inhibits uterine activity, by diminishing the force of contraction and uterine tone, and disturbing the rhythmicity of contraction.

Studies with an intravenous drip of dilute Adrenalin demonstrate, in addition, that recovery of uterine activity from inhibition occurs during a constant rate of administration. Sudden withdrawal of the intravenous drip is followed by a transitory rebound from inhibition, the degree of activity exceeding that seen during the control period.

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A STUDY OF THE HISTOLOGIC STRUCTURE OF THE CERVIX IMMEDIATELY POST PARTUM*

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SINCE Mauriceau,[1] Duncan,[2] and Bandl[3] published their impressions of the functional relationship of the cervix to the lower uterine segment, much work has been done toward the clarification of the anatomy and physiology of these structures. Many investigators have made extensive studies of the gross and microscopic anatomy of the region both in the human being and in the monkey, and as a result the changes in configuration of the uterus, the isthmus, and the cervix itself during pregnancy are reasonably well known.[4-11]

More than a hundred years were necessary to evaluate the anatomic changes in the lower uterine segment which accompany pregnancy, and it is therefore not surprising that the physiology of retraction and dilatation of the cervix has hardly been touched. There are two widely recognized theories concerned with this mechanism: one school has postulated active dilatation of a muscular sphincter; the other adheres to the opinion that the mechanism is passive, merely a mechanical stretching and pulling up of the external os. Most textbook authorities avoid the issue by noncommittal statements on the mechanism of retraction and dilatation. Stieve[11] proposed a theory which is based on careful anatomic and microscopic investigation of the cervical structure. Briefly, he postulated that, following the loss of the mucous plug, there is a sloughing of the greatly hypertrophied mucosa; thus, a sizable opening is produced in the cervical lumen. Pressure of the membranes, or from the presenting part, produces compression of the cervical wall; there is a consequent loss of wall volume through reduction of the amount of blood in the wall, which in his opinion is a corpus-cavernosum-like structure and therefore capable of large changes in volume and rigidity (Fig. 1). Once the lumen is enlarged sufficiently through this mechanism, retraction of the cervix around the presenting part is merely a question of shortening of the lower uterine segment.

Recently Danforth[12] investigated the muscle and fibrous-tissue constituents of the cervix. While offering little comment as to the mechanism of dilatation, he seemed to feel that muscular sphincter action played little part in the opening of the lumen.

While systematically investigating some of the factors which are associated with the mechanism of labor, the cervical alterations were studied. This report is concerned with the histologic alterations in the cervix immediately following delivery of the placenta.

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*The opinions expressed here are those of the author and do not necessarily reflect those of the Navy Department.

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Materials and Methods

This series includes 100 consecutive patients who were considered normal and in whom the length of labor could be reasonably estimated.

All patients had had antenatal care during the greater part of the pregnancy, and the physical condition, the size and configuration of the pelvis, and the presentation of the fetus were known before the onset of labor. All abnormalities of the maternal organism, such as cardiac impairments, toxemias of pregnancy, endocrine or pelvic abnormalities which might influence the type or length of labor, were considered reason for exclusion from this series. Fetal anomalies of being or position, such as twins, monsters, breech, brow, and face presentations, were also eliminated. Patients who came in with the cervix fully dilated and with no record of the physical characteristics of the cervix were not included.

Parity, age, and type of previous labors were noted. The size of the fetus, the estimated amount of fluid in the uterus, and the fetal position and presentation were recorded. The cervix was palpated rectally and the following data recorded: the actual time of examination, the station of the head, the position of the sagittal suture, the cervical dilatation and effacement, and the relative consistency of the anterior and posterior lips of the cervix. This consistency was arbitrarily considered to be one plus if the cervix approximated the feel of the examiner's lower lip, and four plus if it approximated the feel of the cartilage of the nose. Sterile vaginal examinations were done on approximately 50 per cent of the patients at some time during labor in order to confirm rectal data. Rectal findings were obtained and recorded every hour on patients in short labors and at longer intervals on patients in labor for extended periods. The degree of effacement and estimation of consistency of the cervix used for statistical purposes in this report were those obtained in the early stages of labor.

The total length of labor was considered to include the time at which the patient first noted regular painful contractions until the delivery of the placenta. True labor was determined as the length of time from the beginning of progressive dilatation of the cervix to the delivery of the placenta.

Sedation was used on all patients as soon as true labor was assured; it consisted in general of barbiturates, Demerol, and scopolamine. Approximately 10 per cent of the patients were given caudal anesthesia and analgesia; delivery of the patients under routine sedation was accomplished by ethylene and oxygen.

Immediately following the delivery of the placenta, the anterior lip of the cervix was pulled down by means of Allis clamps and a wedge, 1.5 to 2 cm. deep and 1 cm. at the base, was excised with scissors. The biopsies were taken through portions of the cervix which were grossly free of old scars, fresh tears, and other evidence of localized injury and disease. The cut cervix was approximated by two interrupted through-and-through sutures of No. 0 chromic gut. The posterior lip was treated in the same manner, so that in practically all cases there was an anterior and a posterior biopsy.

These wedges were immediately placed in Zenker-formol fixative and left for ten to twelve hours. They were trimmed, and then washed for twenty-four hours in running tap water. Blocks were cut, and the sections carried through 70 and 80 per cent alcohol, where they were stored until they were imbedded in collodion. Sections were cut at six microns and each was stained with both hematoxylin and eosin and with Malloy's connective-tissue stains.

The sections were studied systematically by zones (Fig. 1) and these zones were compared statistically with the clinical aspect of the cervix and the length of labor. The epithelium was considered to be the first zone (Fig. 1, a). Zone 2

consisted of the subepithelial layer (Fig. 1, b). It was bounded on the interior margin by Zone 3, which consisted of a mixture of circular and longitudinal muscle fibers admixed with varying amounts of connective tissue (Fig. 1, c). Zone 4 was the connective tissue layer found at the core of the cervix and bounded by the muscle layer on the outside (Fig. 1, d). It contained most of the vascular elements.

These zones were classified arbitrarily in one plus to four plus, from the least dense in appearance to the most dense. The area covered by a given zone was measured by an ocular micrometer. The depth of Zone 4 was determined by the depth of the section taken. While the epithelial zone was quite sharp, and Zone 2 usually so, it must be emphasized that real difficulties occurred in differentiating Zones 3 and 4, and the depth of staining influenced greatly the apparent density of all zones.
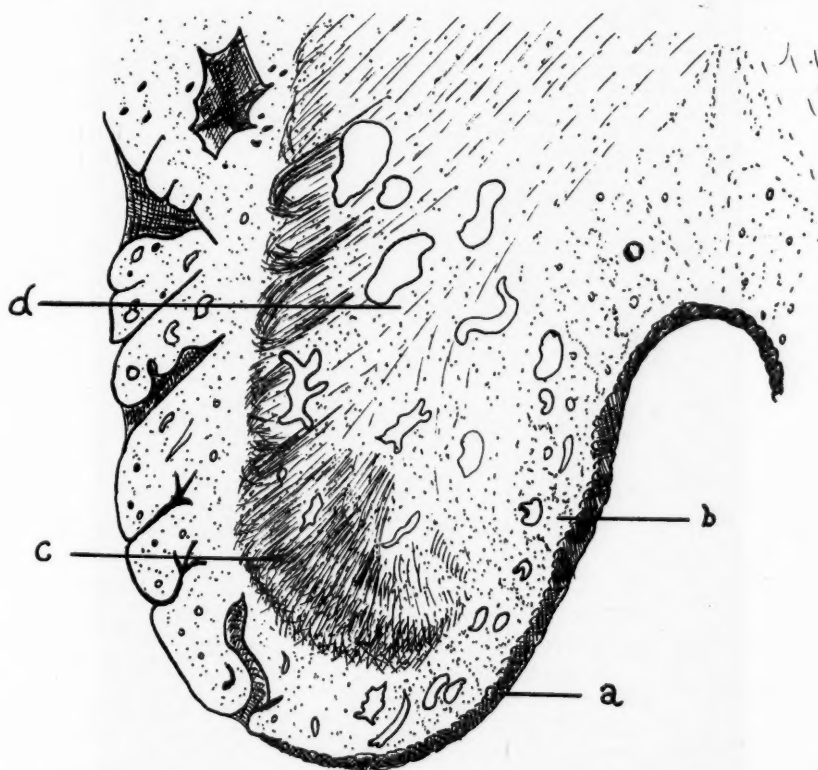

Fig. 1.—A schematic drawing of the histologic structure of the cervix.

a. The layer of squamous epithelium is always present, always sharply defined, and normally varies only moderately in width.

b. The submucous zone is always present, but is quite variable in width, structure, and vascularity.

c. The muscle-containing portion of the cervix is usually present, and fairly well defined only on the peripheral border. The inner border is rarely easily differentiated from the central core of the cervix.

d. The vascular central area or core of the cervix is extremely variable in composition and limits.

Figs. 2 through 7 demonstrate the appearance of the zones described, pointing out the method of differentiating the histologic elements.   (Staining of these tissues was carried out by Mallory's connective-tissue stain.)

Results

The average age of the total group was found to be 25.1 years; the primip-aras averaged 23.7 years and the multiparas 27.2 years. It is probably reason-able to assume that this slight difference in age should not be used to account for any differences found in the cervical tissue.

As has been explained, labor was calculated as *true* labor, defined as the length of time from the beginning dilatation of the cervix to the delivery of the placenta, and as *total* labor, defined as the length of time required to deliver the

Fig. 2.
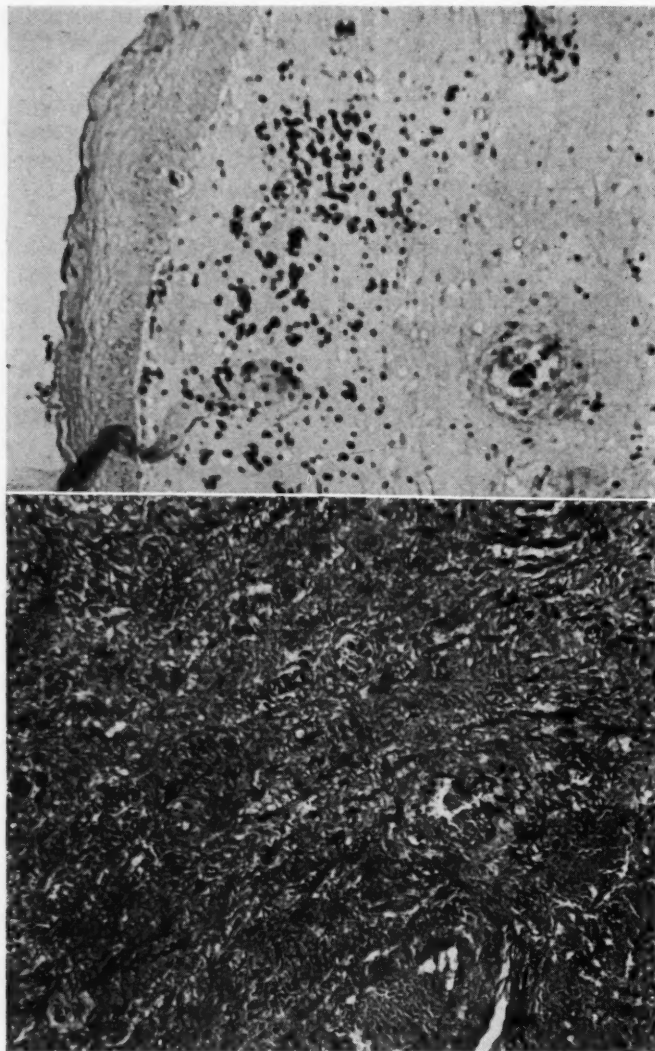
Fig. 3.

Fig. 2.—This high-power microphotograph shows a typical appearance of the squamous epithelium (Zone 1), and a very edematous Zone 2, composed for the most part of loose, thin collagen fibers; vascular elements, and edema fluid. Note the round-cell infiltration. (The degree of rigidity of this zone would be classified as 1 plus).

Fig. 3.—A high magnification of a very fibrous type of Zone 2. Note the contrast with that in Fig. 2. This area is composed of well-knit and very dense collagen. Vascularization is very noticeable, but there is no inflammatory cellular infiltration. This zone was classified as being 4 plus rigidity.

placenta following the onset of painful contractions, as related by the patient.
The average length of total labor was found to be 13.6 hours; there was very
little difference between the primiparous group with an average of 14.5 hours
and the multiparous group with 12.3 hours. The average true labor for the
whole group was found to be 6.7 hours, and a difference of almost 100 per cent
was noted between the two groups. The primiparas were in true labor for an
average of 8.3 hours (Table I).

Fig. 4.
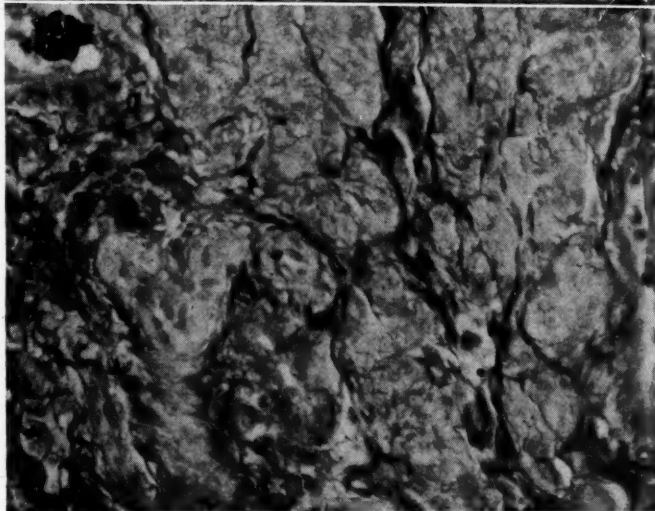
Fig. 5.

Fig. 4.—A high magnification of this cervical tissue in the muscle-containing area.
Zone 3 shows a solid muscle content. Only enough fibrous tissue is in evidence to separate the
muscle bundles. This area would be considered 100 per cent muscle and 3 plus rigidity.

Fig. 5.—A higher magnification of the same area. Fibrous tissue is noted to be at a
minimum.

It has not been possible in this study to correlate the degree of firmness of
the cervix as determined by clinical examination with the length of labor. A
study of Tables II, III, and IV gives one the impression that such a correlation

is possible, but it is evident that the apparent trend toward longer labors in those individuals with firm cervices is in reality a function of the parity and not of the degree of rigidity. That the parity of the patient is the determining variable is borne out by examination of the tabulated data: total labor in the primipara (Table IV), total labor in the multipara (Table V), true labor in the primipara (Table VI), and true labor in the multipara (Table VII).
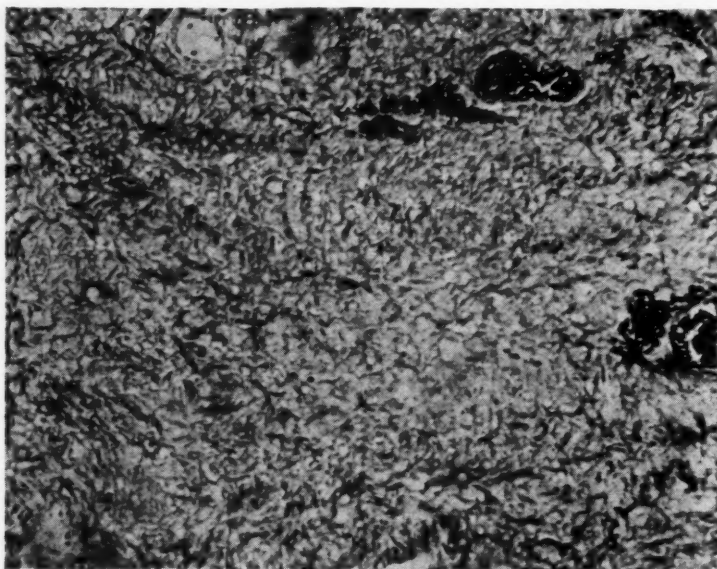
Fig. 6.—A photograph taken from the same zone (3), showing a total lack of muscle fibers. The total area is composed of firm and densely woven collagen. Cellular content is minimal. Muscle content would be zero; rigidity 4 plus.
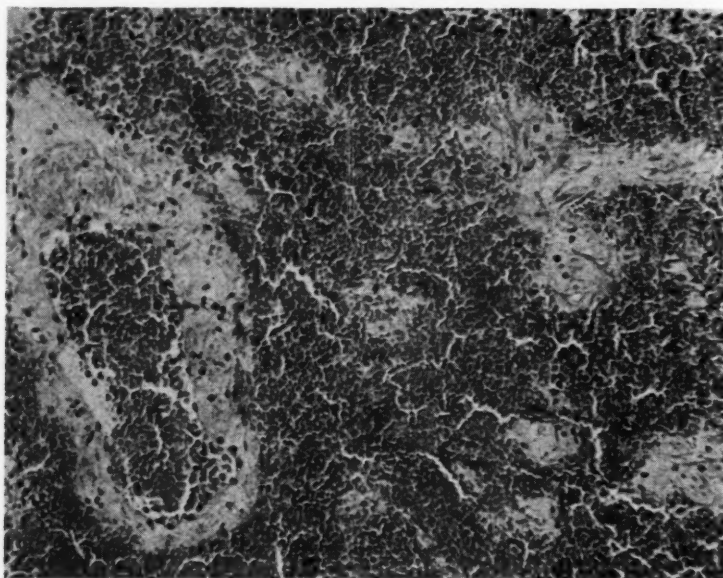
Fig. 7.—This area was taken in Zone 3 of a very edematous and hemorrhagic cervix. There is no identifiable muscle and only small areas of fibrous tissue in bundles form a basic structure for this hemorrhagic tissue. Muscle content is absent and the degree of firmness is classified at 1 plus.

TABLE I. AN ANALYSIS OF THE LENGTH OF TRUE LABOR AND TOTAL LABOR IN BOTH THE
PRIMIPARAS AND THE MULTIPARAS OF THE SERIES

PARITY	NUMBER OF CASES	AVERAGE LENGTH OF TRUE LABOR (HOURS)	AVERAGE LENGTH OF TOTAL LABOR (HOURS)
Multiparas	38	4.4	12.3
Primiparas	54	8.3	14.5
Total	92	6.7	13.6

An attempt was then made to correlate the texture and architecture of the various zones described in the foregoing with the length of labor in the primiparous and in the multiparous woman.

TABLE II. ANALYSIS OF THE MICROSCOPIC PICTURE OF THE DESIGNATED ZONES AND THE
CLINICAL TEXTURE OF THE CERVICES WITH REGARD TO THE LENGTH OF LABOR

| LABOR (HOURS) | PARITY | NUMBER OF CASES | ZONE[1] WIDTH[1] | ZONE[2] | | ZONE[3] | | ZONE[4] | | FIRMNESS (CLINICAL)[3] |
				TEXTURE[2]	WIDTH[1]	TEXTURE[2]	WIDTH[1]	TEXTURE[2]	WIDTH[1]	
4 or less	Multiparas	8	1.4	1.6	7.3	2.8	21	2.2	16	1.8
	Primiparas	3								
5 to 8	Multiparas	13	1.7	1.5	6.6	2.9	16	2.4	20	1.9
	Primiparas	7								
9 to 16	Multiparas	12	1.3	2.1	7.6	2.9	19	2.4	20	2.3
	Primiparas	25								
17 or more	Multiparas	5	1.2	1.7	7.0	2.0	13	2.5	20	2.5
	Primiparas	20								

In this and following tables, *texture* is graded as 1, 2, 3, and 4, and *width* is determined by actual measurement, in arbitrary units of the extent of the zone.

In this and subsequent tables, the following classification obtains:

1. Arbitrary units on an ocular micrometer under low power magnification.
2. Arbitrary units of visual density from + to ++++.
3. Clinical impression graded as + (soft) to ++++ (very firm).

The width and cellular content and type of Zone 1, the epithelial layer, were not different in the two groups save for a definite increase in the incidence of decidual reaction in the multiparas (Tables II and III). The subepithelial layer, designated Zone 2, was not found to differ with parity, and no correlation with the length of labor could be made (Tables II and III).

TABLE III. DATA IN WHICH AN ATTEMPT IS MADE TO CORRELATE THE LENGTH OF TRUE LABOR
WITH THE WIDTH AND TEXTURE OF THE VARYING ZONES AND THE DEGREE
OF CLINICAL FIRMNESS

| LABOR (HOURS) | PARITY | NUMBER OF CASES | ZONE[1] WIDTH[1] | ZONE[2] | | ZONE[3] | | ZONE[4] | | FIRMNESS (CLINICAL)[3] |
				TEXTURE[2]	WIDTH[1]	TEXTURE[2]	WIDTH[1]	TEXTURE[2]	WIDTH[1]	
2 or less	Multiparas	15	1.4	1.4	8.1	2.7	16	2.2	17	2.3
	Primiparas	4								
3 to 6	Multiparas	20	1.4	1.7	6.7	2.9	19	2.4	21	1.8
	Primiparas	18								
7 to 12	Multiparas	1	1.5	2.1	6.7	2.9	20	2.7	21	2.0
	Primiparas	19								
13 or more	Multiparas	3	1.5	1.9	8.0	3.2	18	2.6	25	2.8
		12								
Total		92	1.4	1.8	7.6	2.9	19.7	2.4	20.9	2.1

Because of its suggested importance, the muscular layer (Zone 3) was studied from several points of view: the actual area covered, the relative density of the constituent parts, and the proportion of muscle to fibrous tissue elements in this zone. No correlation between the actual area covered and the proportion of muscle to fibrous-tissue elements could be made in either the primiparous or multiparous woman in either true or total labor. There seems to be a small but possibly significant correlation of the texture of the muscular zone with length of true labor in both the multiparous and primiparous groups (Tables VI and VII). The same seems to be true as to the total labor in the primipara, although no such inference could be drawn for total labor in the multiparous woman (Tables IV and V).

TABLE IV. THE CLINICAL DEGREE OF FIRMNESS, THE MICROSCOPIC TEXTURE, ZONE 3 (MUSCLE-CONTAINING ZONE), THE PERCENTAGE OF MUSCLE-CONTAINING TISSUE (IN RELATION TO THE TOTAL CERVICAL MASS), AND THE PERCENTAGE OF BLOOD-CONTAINING TISSUE (BOTH AS HEMORRHAGIC INFILTRATION AND THAT CONTAINED BY VESSELS) IN RELATION TO THE LENGTH OF TOTAL LABOR IN THE PRIMIPARA

TOTAL LABOR (HOURS)	NUMBER OF CASES	CLINICAL FIRMNESS[3]	MICRO-SCOPIC TEXTURE	ZONE[3]		MUSCLE-CONTAIN-ING TISSUE (PER CENT)	BLOOD-CONTAIN-ING TISSUE (PER CENT)
				TEXTURE[2]	WIDTH[1]		
4 or less	3	1.5	2.6	3.0	23	30	12
5 to 8	7	1.8	2.3	2.5	14	17	38
9 to 16	25	2.5	2.4	2.9	19	38	20
16 or more	20	2.4	2.7	4.0	20	30	16

TABLE V. THE CLINICAL DEGREE OF FIRMNESS, THE MICROSCOPIC TEXTURE, ZONE 3 (MUSCLE-CONTAINING ZONE), THE PERCENTAGE OF MUSCLE-CONTAINING TISSUE (IN RELATION TO THE TOTAL CERVICAL MASS), AND THE PERCENTAGE OF BLOOD-CONTAINING TISSUE (BOTH AS HEMORRHAGIC INFILTRATION AND THAT CONTAINED BY VESSELS) IN RELATION TO THE LENGTH OF TOTAL LABOR IN THE MULTIPARA

TOTAL LABOR (HOURS)	NUMBER OF CASES	CLINICAL FIRMNESS[3]	MICRO-SCOPIC TEXTURE	ZONE[3]		MUSCLE-CONTAIN-ING TISSUE (PER CENT)	BLOOD-CONTAIN-ING TISSUE (PER CENT)
				TEXTURE[2]	WIDTH[1]		
4 or less	8	2.0	2.2	2.8	21	30	12
5 to 8	13	2.0	2.4	3.2	18	30	9
9 to 16	12	2.0	2.5	2.8	20	26	13
16 or more	5	2.4	2.6	2.5	15.5	26	8

Zone 4, that portion of the cervix containing most of the firm and concentrated fibrous tissue and a large portion of the blood-vessel constituents, was analyzed in so far as the actual area covered, relative density of the tissue, and percentage of blood-containing area relative to the whole biopsy specimen. The length of labor, either total or true, could not be correlated with any of these factors. In general, when the amount of blood contained in the specimen was considered, it was found that the primiparous cervix was more vascular than the cervix of the multipara, and that the posterior lip contained more filled blood vessels than the anterior lip.

The muscular layer might be expected to work more efficiently as a sphincter in direct proportion to its size and texture, but such was not the case. Indeed, if any significance can be attached to the slight changes noted in this series, the converse was found to be true. Therefore, it seems reasonable to believe that sphincter action of the human cervix plays no important part in the ease with which the normal cervix dilates.

TABLE VI. THE CLINICAL DEGREE OF FIRMNESS, THE MICROSCOPIC TEXTURE, ZONE 3 (MUSCLE-CONTAINING ZONE), THE PERCENTAGE OF MUSCLE-CONTAINING TISSUE (IN RELATION TO THE TOTAL CERVICAL MASS), AND THE PERCENTAGE OF BLOOD-CONTAINING TISSUE (BOTH AS HEMORRHAGIC INFILTRATION AND THAT CONTAINED BY VESSELS) IN RELATION TO THE LENGTH OF TRUE LABOR IN THE PRIMIPARA

TRUE LABOR (HOURS)	NUMBER OF CASES	CLINICAL FIRMNESS[3]	MICRO-SCOPIC TEXTURE	ZONE[3]		MUSCLE-CONTAINING TISSUE (PER CENT)	BLOOD-CONTAINING TISSUE (PER CENT)
				TEXTURE[2]	WIDTH[1]		
2 or less	4	2.3	2.5	2.0	17	24	22
3 to 6	18	2.0	2.6	2.4	17	32	17
7 to 12	19	2.7	2.6	2.9	20	39	25
12 or more	12	2.6	2.7	3.0	18	18	25

TABLE VII. THE CLINICAL DEGREE OF FIRMNESS, THE MICROSCOPIC TEXTURE, ZONE 3 (MUSCLE-CONTAINING ZONE), THE PERCENTAGE OF MUSCLE-CONTAINING TISSUE (IN RELATION TO THE TOTAL CERVICAL MASS), AND THE PERCENTAGE OF BLOOD-CONTAINING TISSUE (BOTH AS HEMORRHAGIC INFILTRATION AND THAT CONTAINED BY VESSELS) IN RELATION TO THE LENGTH OF TRUE LABOR IN THE MULTIPARA

TRUE LABOR (HOURS)	NUMBER OF CASES	CLINICAL FIRMNESS[3]	MICRO-SCOPIC TEXTURE	ZONE[3]		MUSCLE-CONTAINING TISSUE (PER CENT)	BLOOD-CONTAINING TISSUE (PER CENT)
				TEXTURE[2]	WIDTH[1]		
2 or less	15	2.5	2.3	2.6	16	23	18
3 to 6	20	1.7	2.5	3.1	20	23	6.7
7 or more	4	3.1	2.7	4	20	21	6.2

The size of the blood-containing portion of the cervix was not found to parallel the rapidity of labor. This evidence is considered to be contrary to the substantiation of Stieve's conception of the corpus-cavernosum nature of the cervical wall. Rather, the amount of the blood in the cervix usually parallels the violence of labor and resistance to dilatation afforded by the cervix in these cases.

Discussion

Investigation of the histologic changes in the cervix which accompany labor has failed to show any correlation with the length of labor or with the parity of the subject. Other workers have been able to relate the degree of softening of the cervix as determined clinically with the length of labor, but this correlation seems to depend on palpation of a physiologic change which is not clearly reflected in cellular morphology.[13, 14]

The muscular layer is more efficient as a contraction sphincter in direct proportion to its size and muscle content. If muscle fibers responsible for active dilatation are present, and the existence of such fibers is merely a supposition since they have not been demonstrated, they are too few to be effective except perhaps when the sphincter mechanism is paralyzed. Dilatation of the pupil is effected in such a manner, and it is reasonable to assume that the mechanism of cervical dilatation may be similar. This study tends to show that the mechanism of dilatation of the cervix during labor is either entirely passive or chiefly passive, with relaxation of the sphincter playing the major role and active dilatation playing only a minor role. Retraction of the cervix is accomplished by contraction of the uterine muscle in the lower uterine segment and body of the uterus.

It is felt that this work is of value in the study of labor, however, since several inferences may be drawn from the negative type of evidence obtained. It was not found possible to distinguish by histologic means primiparous cervices from those of the multiparas nor those in either group with long labors from individuals who had sustained rapid delivery. Scarring of the cervix or excess fibrous tissue then seems to play no significant part in the course of cervical dilatation in the average case.

Summary

The relation of the cervix to the length of labor as determined by the histologic structure is reported.

Cervical biopsies, removed immediately post partum from 100 obstetrical patients with uncomplicated labors, were studied in an attempt to correlate the length of labor with the architecture and component parts of the cervical structure.

By the methods employed, it was impossible to relate the length of labor to the quantity or quality of epithelium, fibrous tissue, muscular or vascular elements which go to make up the human cervix.

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PATTERNS OF BRAXTON HICKS CONTRACTIONS AND THE GRADIENT OF UTERINE ACTIVITY DURING THE FIRST STAGE OF LABOR: A STUDY WITH THE MULTI-CHANNEL TOKODYNAMOMETER*

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THE occurrence of nonpainful uterine contractions during the latter part of pregnancy is commonly known to obstetricians. That these occur with increasing frequency as term approaches is likewise generally known. Moreover, the reactivity of the myometrium to posterior pituitary extract increases concurrently with increasing spontaneous contractility in both rabbits (Knaus, 1927; Robson, 1933a) and in the human (Robson, 1933b; Murphy, 1942) as well as in other animal species (Reynolds, 1949a). Only one of these studies was made by external tokography with the intact uterus in women (Murphy, 1942) so only in this instance has it been possible to correlate the characteristics of these Braxton Hicks contractions with the subsequent clinical course of labor. In this work, the claim is made that such a correlation can be made, although one looks in vain for a precise account of the features of prelabor activity which indicate that a labor will be of average duration or will deviate from it, and certainly no yardstick has been presented of the statistical reliability of such a correlation.

With the advent of multichannel tokometry, as opposed to the single-point method of recording employed by Murphy and others, it has recently become possible to record the contraction characteristics in several parts of the uterus simultaneously (Reynolds, Heard, and Bruns, 1947). By application of suitably mounted strain gages, records are made simultaneously on a single piece of moving paper of the intensity, duration, nad frequency of contractions in the uppermost (fundal), middle, and lowermost (lower uterine segment) parts of the uterus. A sample of such a record is shown in Fig. 1. This exemplifies the normal pattern of uterine activity during the first stage of labor when records are made from three points. The contractions in the fundus are stronger and they last longer than in more caudal parts of the uterus. Progress in the first stage of labor is associated with the establishment of such a gradient of activity, and the more definitely it is established in the laboring uterus the more rapidly will the labor proceed (Reynolds, Bruns, and Hellman, 1948). As soon as this fact was appreciated, however, the pertinent question arose, To what extent, if any, is the pattern of uterine contractility in Braxton Hicks contractions related to

the normal gradient of activity of the uterus in labor? The present study is concerned with this problem. It demonstrates that, on the basis of the data so far obtained, there is no correlation detectable between these two conditions. Consequently, local conditions which prevail during labor govern the course of the parturitional process.
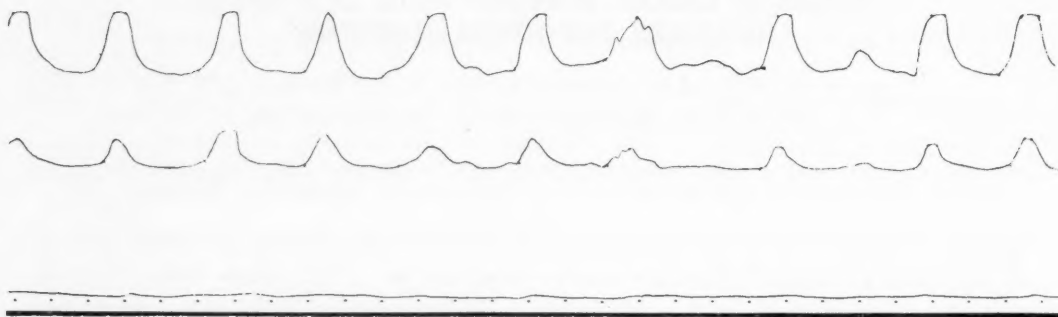

Fig. 1.—Excerpt of a record from the first stage of true labor recorded by a three-channel TKD. Top, fundus; middle, mid-part of uterus; bottom, lower part of uterus, above symphysis pubis.
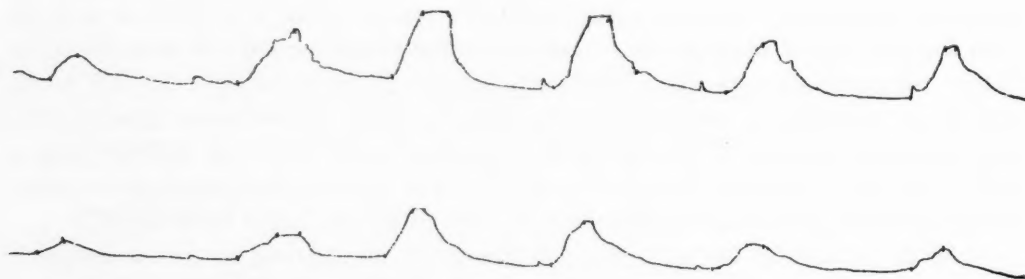

Fig. 2.—Excerpt from a record of Braxton Hicks contractions as recorded with the two-channel TKD. Top, fundus; bottom, lower part of the uterus.

Methods

Apparatus.—A two-channel, ink-writing recorder was used in conjunction with two Statham strain gage dynamometers (Model G1-4-250) with a range of ±120 grams. These are mounted on brass rings, held to the abdomen by means of double-coated Scotch tape. An adjustable plunger in the center of the ring transmits pressure from the contracting uterus beneath to the sensitive pin of the gage. The power supply is exactly as described in other communications (Reynolds, Heard, and Bruns, 1947; Reynolds, Bruns, and Hellman, 1948) except that it contains an electrical standardization feature which permits one to calibrate the apparatus at any time, and to adjust the sensitivity so that a deflection of 10 millimeters of the scale is equal to 60 grams of pressure applied on the strain gage. Two Brush Development Company DC amplifiers (no. BL 913) and a Double Channel Magnetic Oscillograph (no. BL 202 modified with a slow-speed motor to give a paper speed of 1 inch per minute (10 r.p.m.) were used.

A typical record obtained with this unit of Braxton Hicks activity of the uterus is shown in Fig. 2. The intensity, duration, contraction time, and frequency characteristics of the two parts of the uterus (fundus, lower uterine segment) are seen. All records were continued for twenty or more minutes, in multiples of twenty minutes. The average intensity, duration, and frequency of the contractions per twenty-minute period were determined. It is these figures which are given in the tables and upon which the graphs are based.

In all, seventy-four patients were employed in this study. They were individuals who appeared in the prenatal clinic of the Cumberland Hospital. In only a few cases was more than one record of uterine activity obtained prepartum. In seventeen of these cases, records were obtained during the first stage of labor. The earliest time that records were obtained was the twenty-first week of pregnancy. One to two records were obtained for most weeks up to the twenty-ninth week of gestation. Five to twelve records for each of the remaining weeks till term were obtained. All patients from whom the data are used in this study were normal from the obstetric viewpoint, being free of preeclampsia and toxemia, hydramnios, and cephalopelvic disproportion. All deliveries were normal and commenced spontaneously although records during labor were not usually made. A general summary of the results is given in Table I.

Results

Patterns of Activity.—The positions of the leads (pickoffs) were consistently in the middle of the upper third of the uterus and near the middle of the lower half of the uterus, above the level of the symphysis pubis. In no record obtained prior to the thirtieth week of pregnancy were any Braxton Hicks contractions recorded. This is interesting in view of the fact that records up to an hour or more in duration were obtained, and the strain gages are sensitive to pressures of less than one gram. Thus we conclude that the uterus does not commonly manifest appreciable activity prior to the thirtieth week of gestation. Of five records obtained in the thirtieth week, two showed activity in the lower uterine segment only, the other three, no activity whatever during the period of observation. Mention may be made parenthetically that it is not uncommon to observe throughout the uterus that small, minor, rhythmic undulating contractions may be seen in the uterus, occurring at a frequency of about 60 seconds. These may be present by themselves, or associated with the major Braxton Hicks contractions which are the main subject of this paper. The cause and functions of the undulating contractions may not be surmised at this time.

However, inactive uteri during the period of recording are seen until the thirty-eighth week. The contractions, when present, generally are stronger in the fundus than in the lower part of the uterus (Fig. 3). During the thirty-ninth week, no records of inactive uteri were obtained in twelve patients and, generally speaking, the average strength of contractions in the fundus is greater than a week earlier. The general situation during the first stage of labor, it will be recalled, is that there is a gradient of contraction in the uterus which gives rise to fundal dominance. There is no significant contractility in the lower uterine segment. The duration of contractions in the fundus likewise exceeds the duration of contractions occurring in the lower uterine segment (Fig. 4). Inasmuch, therefore, as intensity and duration are the essential components of muscular work, we see that throughout the last quarter of pregnancy there is a gradient of myometrial work from above, downwards, and that a general feature of this is that it tends, on the average, to become progressively stronger as term approaches. With the onset of labor, however, the activity of the fundus continues strong, while the lower part of the uterus becomes inactive (Reynolds, Hellman, and Bruns, 1948).

TABLE I. BRAXTON HICKS CONTRACTION CHARACTERISTICS*

WEEKS	NO. PATIENTS	ACTIVITY CHARACTERISTICS	INTENSITY (GRAMS)			DURATION (SECONDS)			FREQUENCY (CONTRACTIONS PER HOUR)
			FUNDUS SEGMENT	MIDDLE SEGMENT	LOWER SEGMENT	FUNDUS SEGMENT	MIDDLE SEGMENT	LOWER SEGMENT	
21	2	None except fetal movements							
23	1	No activity							
24	1	Not regular (short labor 5 hours)		21			44		6
27	1	No activity							
28	1	Regular		153	42		54	34	2
29	2	1. No recorded activity 2. Regular (6 hour labor)		5 (0-33)			16		2 (0-4)
30	5	1. Not regular in size and frequency 2. Regular activity 3. One 20-minute period, fetal activity only 4. Not regular 5. No activity		32 (0-68)	11		22	8	5 (0-11)
32	3	1. Fetal activity not regular 2. Fairly regular 3. Fetal activity	9	(0-28)	6	13		10	2 (0-6)
33	11	1. Good activity 2. Regular but no activity 3. Not regular. More activity in lower part 4. Very regular 5. Fairly regular 6. Not regular 7. Not regular 8. Regular 9. Not regular 10. Slight irregular activity in fundus and lower uterus 11. Not regular	25	8 (0-67)	14	23	11	14	6 (1-13)
34	8	1. No measurable contractions (4½ hours short labor) 2. No activity 3. Last 6 minutes very regular 4. Very regular 5. Regular 6. Contractions small ripples (short labor, three and one-half hours) 7. No activity 8. Not regular, was active	12		3 (0-47)	9		4	4 (0-11)

Case	n						
35	9	24	9	21 (0·85)	7	26	15	4 (0·22)
36	4	23		2 (0·54)		37	5	7 (0·7)
37	5	17		32 (0·142)		11	13	5 (0·14)
38	12	23		3 (0·111)		22	9	7 (0·21)
39	9	51	4	31 (0·117)	5	32	22	--
Contractions in labor	17	51	-	25 (3·91)	-	38	20	--

35
1. Not regular (short labor 2 hours)
2. Not regular
3. Not regular
4. Fairly regular
5. Only one contraction
6. Not regular
7. Not regular
8. Long record, irregular activity
9. Regular

36
1. Not regular
2. Not regular
3. Slight irregular activity
4. Active fetus but no contractions

37
1. No comment
2. Fetal activity, one contraction
3. Active fetus but no contractions
4. Not regular
5. Not regular

38
1. No comment
2. No comment
3. Irregular
4. Irregular
5. Irregular
6. One big contraction
7. Not regular
8. Nothing to analyze
9. No comment
10. Irregular
11. No activity
12. Regular

39
1. No comment
2. No comment
3. No comment
4. No comment
5. No comment
6. No comment
7. Fetal action and small contraction
8. No activity (short labor)
9. Active (short labor)

*Average values, plain figures; range, in parentheses. The term "No comment" signifies that there was no especially significant feature of the record to be noted.
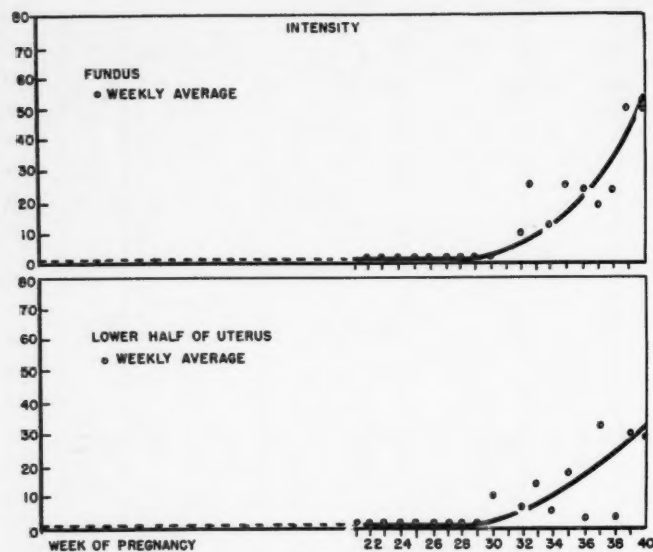
Fig. 3.—Intensity of Braxton Hicks contractions recorded in the upper (top) and lower (bottom) part of the uterus in different weeks of pregnancy. Circles, average values for weekly recordings.
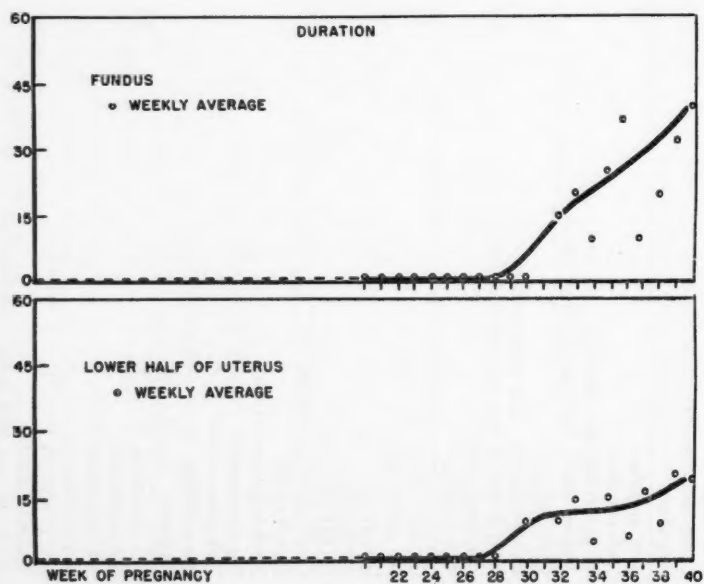

Fig. 4.—Duration of Braxton Hicks contractions recorded in the upper (top) and lower (bottom) part of the uterus in different weeks of pregnancy. Circles, average values for weekly recordings.

What is the frequency with which Braxton Hicks contractions are likely to be observed in different women in any given period of recording?

Percentage Occurrence of Braxton Hicks Contractions.—Fig. 5 shows the frequency of occurrence of Braxton Hicks contractions during the last nineteen weeks of pregnancy. In comparison with the data submitted by Murphy, shown
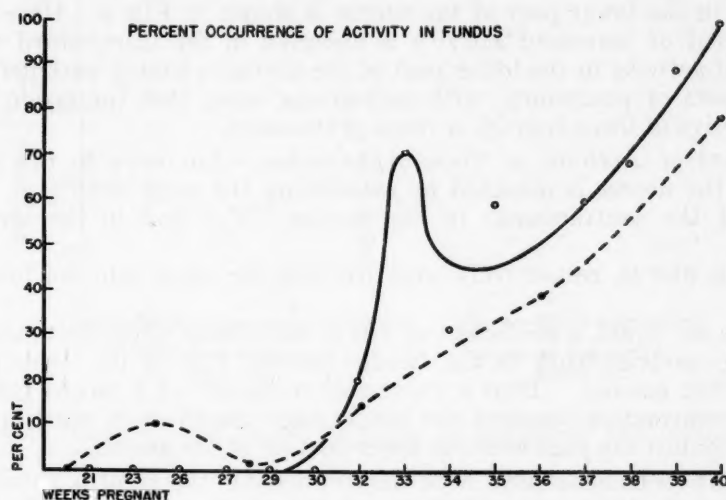

Fig. 5.—Frequency of occurrence if Braxton Hicks contractions during the last nineteen weeks of pregnancy in upper part of uterus. Solid line data obtained in this study (circles, average weekly values); broken line, frequency of occurrence as observed by Murphy who employed a single point external tokograph.
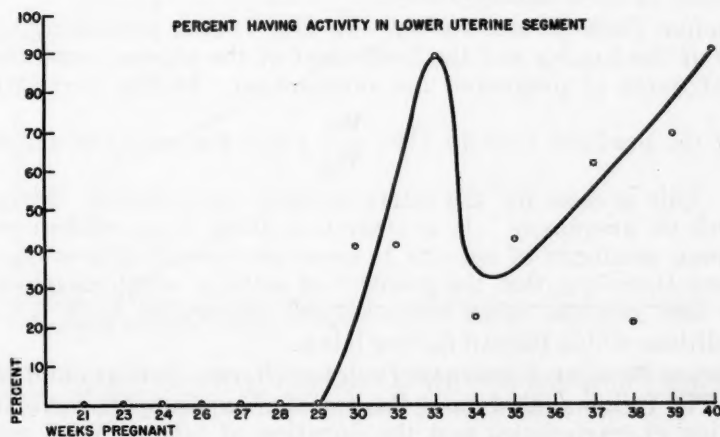

Fig. 6.—Frequency of occurrence of Braxton Hicks contractions in lower half of the uterus. Circles, weekly average values.

also in Fig. 5, we see that the multichannel tokodynamometer yielded a curve only approximately comparable to the one obtained by that investigator. In the first place the incidence of activity is higher during the last six or seven weeks of pregnancy with the TKD than with the Lorand tokograph as used by Murphy. After the commencement of major Braxton Hicks contractions during the thirtieth week of gestation, an increasing number of individuals manifest such

activity. We did not observe, as did Murphy, a progressive increase from then until term, however. In Figs. 5 and 6 it will be seen that in both the upper and lower parts of the uterus, a transient period of increased incidence of Braxton Hicks contractions occurs until the thirty-third week, with a decrease in frequency again in the thirty-fourth week. From this time on, there is a progressive increase in the incidence of Braxton Hicks activity in most uteri until term. As noted, their intensity increases as the end of pregnancy nears. The incidence of activity in the lower part of the uterus is shown in Fig. 6. Here too, a temporary period of increased activity is observed in the thirty-third week. The incidence of activity in the lower part of the uterus is highly variable during the last ten weeks of pregnancy, with indications being that the lower half of the uterus is active in three-fourths or more of the cases.

Gradient of Activity as Term Approaches.—An index to the gradient of activity in the uterus is obtained by calculating the work done (i.e., intensity × duration of the contractions) in the fundus (W_F) and in the lower portion (W_L) of the uterus, respectively, and dividing the latter into the former ($\frac{W_F}{W_L}$).

When these are equal, a coefficient of 1 is obtained and when the number exceeds this, the myometrial work in the fundus exceeds that of the lower part of the uterus by that amount. Thus a numerical coefficient of 4 means that the work of uterine contractions against the strain gage placed upon the fundus is four times that against the gage over the lower portion of the uterus.

Gradient coefficients have been determined for the records obtained in this study during the thirty-seventh, thirty-eighth, thirty-ninth, and fortieth weeks of gestation and they have been considered with respect to parity. The data, when correlated with respect to the duration of labor and the parity of the individuals, give no indication that the gradient characteristics of Braxton Hicks contractions during the last four weeks of pregnancy bear any relation to the duration of labor subsequently.

Contraction Patterns and Parity.—In Fig. 7, data pertaining to parity and the activity of the fundus and the lower part of the uterus, respectively, during the last four weeks of pregnancy are summarized. In this, correlation between an index of the gradient activity (i.e., $\frac{W_F}{W_L}$) and the parity of the individual is attempted. This is done for the thirty-seventh, thirty-eighth, thirty-ninth, and fortieth week of pregnancy. It is clear that there is no evident tendency for weak or strong gradients of activity to occur as a result of previous pregnancy. This suggests, therefore, that the gradient of activity which clearly is important during the first stage of labor to accomplish obstetrical work is the result of uterine conditions which prevail during labor.

Correlation Between Segmental Prelabor Uterine Activity and the Duration of Labor.—Fig. 8 shows the data of this series of experiments correlated in terms of contraction characteristics and the duration of labor. With respect to the fundus, but one relationship suggests itself: If the contractions are intense in the fundus during the thirty-eighth week, the longer is the duration of labor. The same cannot be said for any other week of gestation studied and it is our opinion that the apparent relationship during this one week is probably a fortuitous one. Inspection of our data with respect to activity in the lower uterine segment similarly shows that there is no correlation between the activity in this part of the uterus and the duration of labor subsequently. All in all, therefore, it appears that neither the character nor frequency of Braxton Hicks contractions in any part of the upper or lower part of the uterus foretells the charac-

teristics which the uterus will exhibit later when it is in labor. Again we see that the immediate pattern of uterine activity during labor is governed by conditions prevailing during labor.
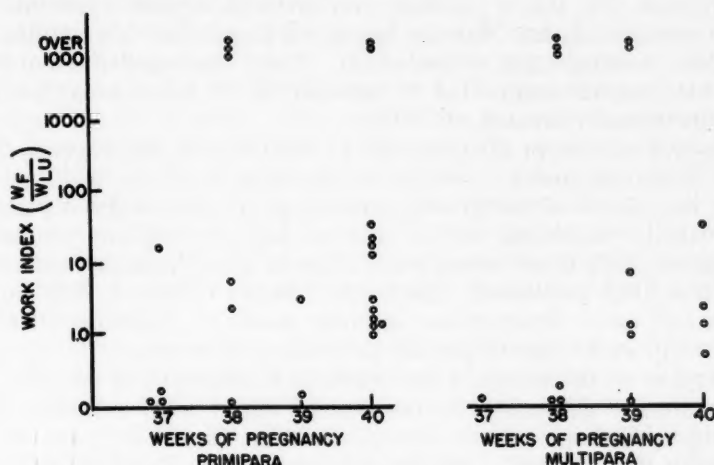

Fig. 7.—Absence of correlation between the work gradient in the uterus (work in fundus divided by work in lower uterus) according to primiparity and multiparity in the last four weeks of pregnancy.
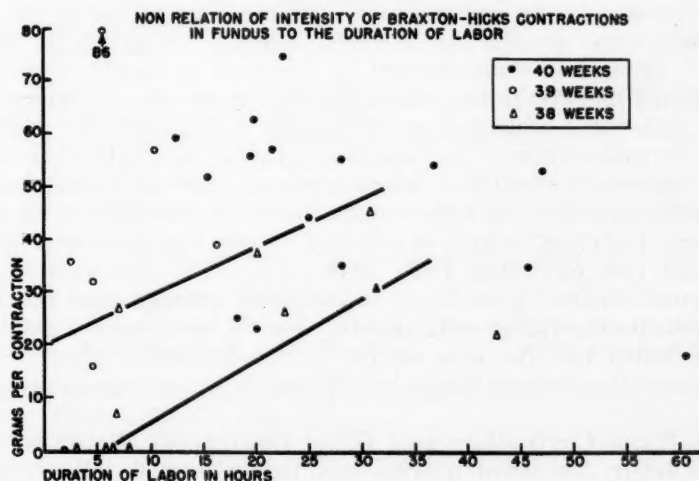
Fig. 8.—Absence of correlation between the intensity of Braxton Hicks contractions at different weeks of pregnancy and the duration of labor. Lines show possible correlation between intensity of activity and duration of labor in thirty-eighth week.

Comment

Discussion of the above results may profitably be confined to three points, namely: (1) the failure to confirm Murphy with respect to the prognostic value of Braxton Hicks contractions concerning the future duration of labor; (2) the basis for a tendency to increased activity of the uterus during the seventh lunar month; and (3) the change which of necessity takes place in the pattern of Braxton Hicks contractions with the onset of labor if the lower part of the uterus has been active.

Prognostic Value of Braxton Hicks Contractions.—Little may be said concerning this point since the difference in viewpoint between ourselves and Murphy is factual: he believes that a single point tokographic record obtained externally some time before term is of value in predicting the duration of labor; we see no evidence that this is possible, even with multipoint external tokography. It should be mentioned that Murphy has not defined what his criteria for a prognosis are when making such a prediction. Until such a definitive statement is made, therefore, we are compelled to consider that a labor prognosis based upon external hysterography is most unlikely.

Transitory Increase in Braxton Hicks Activity in the Seventh Month.—To discuss this point adequately, would, in the opinion of the authors, necessitate an extensive discussion of the growth pattern of the uterus during gestation, and of the hydrostatic conditions in the uterine wall throughout pregnancy. This would rest upon work based upon conditions in litter-bearing animals and monkeys which has been published (Reynolds, 1949b; Gillespie, Ramsey, and Reynolds, 1949) and upon observations recently made by Gillespie (1949) upon the pattern of uterine enlargement during pregnancy in women.

With respect to the comparative work, it is sufficient to say that the period of extensive uterine growth precedes that of rapid fetal growth. As a result, certain changes in shape of the uterus occur in the latter part of pregnancy which affect the tension* and thickness of the uterus. The former increases, and the latter diminishes as the uterus is stretched by the growing fetus in the latter part of pregnancy. In the human being the pattern of uterine enlargement is unique among all the forms studied. It is complex. Elongation of the uterus commences between the twentieth and twenty-first week and at this time it involves incorporation of the *isthmus uteri* into the body of the uterus (Ivy, 1942). This coincides with, or slightly follows, onset of rapid fetal growth. The "elongation" process is characterized by increase in length of the uterus and also by continued increase in the transverse diameter. By the thirty-second week, the limit of transverse widening of the uterus is approached. Further uterine enlargement is predominantly the result of increase in length of the uterus alone.

Clearly, as in the case of all other types of uteri in which detailed studies have been made, approach of suhc tension limits is associated with a local tissue vascular crisis (ischemia) which is relieved by establishment of another pattern of enlargement (see Reynolds, 1946, 1949a, b). It is not surprising, therefore, that the uterus manifests a tendency to increased activity as it reaches one limit of enlargement during the seventh month. By the same token, too, the increased stretching to which the uterus is subjected longitudinally after this time could serve to augment the activity which is observed in the uterus as pregnancy comes to an end.

Braxton Hicks Contraction and Labor Contraction Patterns.—During the first stage of labor, the lower uterine segment is inactive (Reynolds, Hellman, and Bruns, 1948; Hellman, Harris and Reynolds, 1950) while the activity of the uppermost part of the uterus is highly active. Records of patterns of electrical activity of the human uterus confirm this observation also (Steer and Hertsch, 1950). After the cervix is 5 cm. dilated (i.e., 70 to 75 per cent of the duration of the first stage of labor), the activity in the uppermost part of the fundus becomes very strong. This pattern stands in contrast to the general pattern of

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*The term *tension* should be understood in order that this discussion be clear to the reader. In a hollow viscus tension is the force within the tissue which resists further expansion and differs from pressure *within* the organ. It is the result of two principal conditions: (1) the structure (histological components of the tissue) and functional capability (metabolism, hormone control, etc.) of the tissue and, (2) the physical conditions which prevail (*pressure* within the organ, in this case intrauterine pressure, and the *radius of curvature*). In a spherical elastic body, tension equals $\frac{r^2.p}{2}$; in a cylindrical hollow elastic body, one tension component is r.p. For a full discussion, see Reynolds, 1949a.

Braxton Hicks contractions described in this paper, in which the entire uterus is frequently active, especially in the week or two before term. What factors contribute to a change over from one pattern, which is compatible with maintenance of gestation, to the other, which is not? Again, correlations of a speculative sort must serve to point to a possible answer.

As the fetus becomes bigger, the uterus longer, and the uterine wall thinner, two concomitant changes take place. The contracting muscle of the uterus will be gathered up toward the fundus by brachystatic shortening of the fibers lying along the length of the uterus. As a result, the lower uterine segment becomes thinner (i.e., mecystatic lengthening). Second, the growing fetus will stretch the uterus in its thinnest parts, so that they will tend to become thinner. This result is assured, under normal circumstances, because the intense contractions in the fundus prevent this part of the uterus from giving away before the growing fetus. In consequence, therefore, the contractile power of the lowermost part of the uterus is abolished, as observation has demonstrated and as reason would seem to require.

The phenomenon of cervical change, commonly known in clinical circles as "ripening" of the cervix is a consequence of these changes. The condition of increased occurrence and the pattern of increasing intensity, especially in the fundus, appear, therefore, to prepare the uterus for the normal onset of labor with its own particular pattern of myometrial coordination. In this sense, therefore, Braxton Hicks contractions affect the duration of gestation, and they do set the stage upon which the act of labor is played. They are not of prognostic value in this regard, however.

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PENICILLIN THERAPY OF THE SYPHILITIC PREGNANT WOMAN: ITS PRACTICAL APPLICATION TO A LARGE URBAN OBSTETRICAL SERVICE

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THE excellent results obtained in the prevention of prenatal syphilis by treatment of the syphilitic pregnant woman with penicillin has been brought forth in several previous papers. These publications for the most part have dealt almost exclusively with the management of the pregnant woman with infectious syphilis and therefore represent a selected group not typical of the problem found in the average obstetrical practice where most syphilitic women have symptomless syphilis in the early or late stages of the disease. Less attention has been given to the application of this antibiotic to the over-all problem of controlling the transmission of syphilis to the fetus in a routine manner in a large obstetrical service where the prevalence of syphilis is high.

Material

In an effort to study the practical aspects of this problem and to estimate the results to be anticipated we have analyzed the cases at the Philadelphia General Hospital since routine treatment of the syphilitic pregnant woman with penicillin was commenced in September, 1946. Throughout this study we have used a total dosage of 2.4 million Oxford units of aqueous penicillin (crystalline G) given intramuscularly in 60 individual doses of 40,000 units each every three hours (7½ days). We chose this dosage because previous work had seemed to indicate that this was optimal for the prevention of congenital syphilis. This assumption was further borne out as correct in the reports at the symposium on "Recent Advances in the Study of the Venereal Diseases," held in Washington in April, 1949.[1] Until the time of compiling these data, 281 pregnant women in all stages of syphilis had been treated with the penicillin course above outlined, without regard for previous medical handling with respect to this infection. Some of the women had recent infections with no previous treatment, others had infections of long standing with and without antecedent arsenical and bismuth therapy. There are included in this report syphilitic deliveries up to April 1, 1948. The ensuing time was allowed to permit adequate medical follow-up of the newborn infant to determine the presence or absence of syphilis. It is generally felt that this can be decided usually by the age of two months but with certainty in the first six months of life.

In addition to the foregoing we have observed without specific treatment 73 pregnancies in women who were treated for syphilis with penicillin prior to conception. Thirteen of these women were treated during a previous pregnancy, while in sixty cases this was the first pregnancy subsequent to the com-

pletion of penicillin treatment. Two of these patients have gone through two pregnancies each without benefit of further specific therapy.

To evaluate even more thoroughly the results of penicillin therapy we have exercised three types of clinical control not generally employed in previous studies, but which we feel are essential for properly understanding the value of this new remedy. First, we have determined the outcome, satisfactory or unsatisfactory, of pregnancies in the obstetrical service as a whole with the syphilitic group excluded, for the period of this study. Second, we have determined the outcome of pregnancy among a group of syphilitic women who delivered during the period of this study without receiving any antisyphilitic therapy whatever. Third, we have analyzed the outcome of 390 pregnancies (401 infants) in which the syphilitic mother had been treated with varying amounts of arsenical and bismuth in the years just prior to the advent of penicillin treatment.

The Control Groups

The outcome of pregnancy at the Philadelphia General Hospital from Jan. 1, 1945, through March 31, 1948, in *nonsyphilitic* mothers as compared to untreated syphilitic pregnant women is illustrated in Table I. The results of

TABLE I. OUTCOME OF PREGNANCY. UNSELECTED NONSYPHILITICS COMPARED TO UNTREATED SYPHILITICS AT PHILADELPHIA GENERAL HOSPITAL, JAN. 1, 1945, THROUGH MARCH 31, 1948

OUTCOME OF PREGNANCY	SYPHILIS STATUS							
	NONSYPHILITIC PREGNANCIES		UNTREATED SYPHILIS WITH PREGNANCY					
			EARLY SYPHILIS				LATE SYPHILIS	
			SYMPTOMATIC		LATENT			
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Normal living infants	4,902	87.6			16	29.6	13	92.9
Syphilitic living infants			4	57.1	17	31.4		
Neonatal deaths	170	3.0	1	14.3	3	5.5		
Stillbirths	44	.8	2	28.6	9	16.7	1	7.1
Premature infants	160	2.9			4	7.5		
Miscarriages	320	5.7			5	9.3		
Total	5,596	100.0	7	100.0	54	100.0	14	100.0

5,596 nonsyphilitic deliveries show that the anticipated unsatisfactory outcome of pregnancy is 12.4 per cent. There resulted 87.6 per cent normal full-term living infants without any consideration of the effects of syphilis. Comparison with tabular results subsequently to be presented shows that disasters are no more frequent in adequately treated syphilitic pregnant women than they are in the nonsyphilitic group.

The unsatisfactory outcome is high when we are concerned with early untreated syphilis in the pregnant woman. It is observed that no normal living infants resulted from untreated infectious syphilis, and the percentage of living children with congenital syphilis born of untreated mothers with early latent syphilis is 31.4 per cent. The percentages of stillborn infants in these two categories are also extremely high. These two columns are combined in subsequent tables and designated as early syphilis. That 75 women received no needed treatment for syphilis during their pregnancies is noteworthy in an area with an active public health venereal disease control program and with laws in effect requiring prenatal and premarital examinations. Many women

are still admitted to the Philadelphia General Hospital with little or no pre-
natal care. In the practical application of our scientific knowledge on a broad
community basis we are still a long way from the ideal.

The majority of the women observed at this institution are free patients,
coming from the lowest economic stratum in the city. Of the total group of
820 women, 801 were Negro and 19 white. These factors should be considered
in reviewing these statistics since they undoubtedly make for greater lack of
cooperation and possibly also for a poor response of maternal syphilis to treat-
ment or higher incidence of clinical or serologic progression or relapse.

In the group of 75 untreated syphilitics, 68 (90.4 per cent) had either
symptomless (latent) or late syphilis (more than four years' duration). Of
the 338 patients in the penicillin-treated groups, 319 (94.3 per cent) had di-
agnoses of latent or late syphilis, while in the control group receiving "rou-
tine" arsenic and bismuth therapy for syphilis, among 368 patients, 348
(94.8 per cent) fell into this category. This is an even higher percentage of
asymptomatic syphilis complicated by pregnancy than was recently estimated
by Ingraham,[2] who calls attention to the fact that the usual criteria for the
evaluation of any form of antisyphilitic therapy are not applicable to latent
or late syphilis. There are no infectious lesions whose healing we can observe,
nor can we measure response by the rapid fall in titer of the blood serologic
test, since in latent and late syphilis this response is slow and incomplete.
Therefore, the outcome of pregnancy is often our only measuring stick as to
the effectiveness of treatment.

Of the 267 syphilitic women (excluding 14 mothers with congenital syph-
ilis) treated with penicillin during pregnancy, 95, or 35.6 per cent, were sero-
negative or had a Kahn titer of less than 4 units at the time penicillin was
given. Only 26.9 per cent of the 172 who had strongly positive Kahn titer
tests at the outset had become seronegative or attained a Kahn titer of less
than 4 units at delivery. There were 71 syphilitic women (excluding 3 moth-
ers with congenital syphilis) who had received penicillin prior to conception
but not during pregnancy. Fifty-two per cent of these patients had a Kahn
titer of less than 4 units when they registered in the prenatal clinic. Of the
remaining 34 patients who had a titer of 4 Kahn units or more when they
came under our observation during pregnancy, only 14, or 41 per cent, had
shown an appreciable drop in quantitative titer by delivery, yet in this latter
group they were on the average 436 days post penicillin.

The third type of clinical control mentioned above, namely, the outcome
of pregnancy in women with early syphilis treated with varying amounts of
arsenical and bismuth preparations, either prior to or during pregnancy or
both, is shown in Table II. Arsenical and/or bismuth therapy will hereafter
be referred to as "routine" therapy. Patients treated by us during preg-
nancy received neoarsphenamine in dosage ranging from 0.3 to 0.45 Gm.
weekly, depending on tolerance. Adequate therapy prior to pregnancy has
been arbitrarily set at twenty weeks of arsenical and twenty weeks of bis-
muth or equivalent. Adequate therapy during pregnancy has been arbitrarily
considered to be ten weekly injections of arsenical or its equivalent given any
time during the pregnancy with or without bismuth preparation. One hun-
dred ninety-four pregnant women with early syphilis delivered 198 infants
(4 sets of twins) during the period from Jan. 1, 1945, through August, 1946.
As will be done in future tables we have combined primary and secondary
syphilis with early latent syphilis (of less than four years' duration) because
of the relatively small numbers of patients with open lesions and the strong
likelihood, as shown in the control group, that untreated pregnant women
with early latent syphilis will give birth to dead or diseased children. Ten

pregnant women with open lesions of early syphilis were treated during this period. The birth of two living syphilitic infants and one neonatal death (a 4-day-old premature infant) occurred in this group. Both syphilitic infants were born of mothers who reported late in pregnancy and each of whom had received only one injection of neoarsphenamine prior to delivery. Six mothers in this group who had normal living infants had reported relatively early in the pregnancy and had received a total of ten or more injections of arsenicals during pregnancy, but one mother who had received only four injections of neoarsphenamine and one injection of bismuth subsalicylate in oil also gave birth to a normal infant. In addition, for statistical purposes, we have combined those patients who received adequate "routine" therapy during their pregnancy, irrespective of the amount of previous treatment received, inasmuch as, analyzed separately, there was no statistical significance between the mothers who had received little or no treatment prior to pregnancy and those who had adequate treatment before becoming pregnant, provided treatment was adequate during the pregnancy. We have also combined for statistical purposes those mothers who had received adequate therapy prior to pregnancy, irrespective of the amount of treatment they were given during pregnancy, as there were no syphilitic infants in this group. These findings are in agreement with those of Goodwin and Farber[3] as discussed in more detail later.

It is seen in Table II that the majority of syphilitic infants were born to mothers receiving inadequate "routine" therapy, whether this occurred prior to pregnancy or during pregnancy. Two syphilitic infants, however, were born of mothers who received adequate "routine" treatment during pregnancy as will be noted in the next-to-the-last column of the table. Both of these women had early latent syphilis and were still seropositive at the time of delivery. One was a 19-year-old Negro woman who received ten injections of neoarsphenamine (0.45 Gm. each) during pregnancy, and the other was a 21-year-old Negro woman who had received two injections of bismuth before pregnancy and twelve injections of neoarsphenamine (0.45 Gm. each) during pregnancy. The combined failure rate in terms of living syphilitic infants for the entire group treated with varying amounts of arsenic and bismuth is 5.5 per cent. Relatively small amounts of treatment are effective in preventing infection of the fetus as is shown by the fact that even a small amount of treament before pregnancy was sufficient to give almost 60 per cent normal living infants. Adequate treatment before pregnancy is just as effective if not of more value than treatment during pregnancy. When the expectant mother has active early syphilis, arsenical and bismuth therapy delayed till late pregnancy is sometimes insufficient to prevent syphilitic infection of the infant. Seventy-nine per cent of these infants were followed for more than two months while forty per cent were followed for from six to twelve months. With the detailed diagnostic studies employed, including repeated blood serologic tests with quantitative titer if positive and roentgenograms of the long bones as indicated, in addition to physical examination, this amount of medical follow-up was sufficient to determine the syphilis status of the infant in almost every case.

There were 174 pregnant women with late syphilis not included in Table II who delivered 180 infants (6 sets of twins) during this period. They received varying amounts of "routine" therapy either prior to or during pregnancy. No living syphilitic infant resulted. There were 4 neonatal deaths, a percentage of 2.2 as compared to 3 per cent in the nonsyphilitic control group. The percentage of stillbirths, however, was abnormally high, being 5.6 per cent (10 stillborn infants) as compared to less than 1 per cent in the nonsyphilitic group. Further analysis disclosed that one patient had a placenta previa,

TABLE II. OUTCOME OF PREGNANCY FOLLOWING ROUTINE ARSENICAL AND BISMUTH THERAPY FOR EARLY SYPHILIS AT THE PHILADELPHIA GENERAL HOSPITAL, JANUARY, 1945, TO AUGUST, 1946, INCLUSIVE, COMPARED WITH SIMILAR GROUP OF UNTREATED PREGNANT SYPHILITIC MOTHERS

	TREATMENT STATUS											
OUTCOME OF PREGNANCY	UNTREATED BEFORE OR DURING PREGNANCY 60 MOTHERS 61 INFANTS		UNTREATED IN PREGNANCY INADEQUATE BEFORE 17 MOTHERS 17 INFANTS		INADEQUATE IN PREGNANCY				ADEQUATE IN PREGNANCY IRRESPECTIVE OF ANTECEDENT THERAPY 80 MOTHERS 81 INFANTS		ADEQUATE BEFORE PREGNANCY LITTLE OR NO TREATMENT DURING PREGNANCY 31 MOTHERS 32 INFANTS	
					NONE BEFORE 36 MOTHERS 37 INFANTS		INADEQUATE BEFORE 30 MOTHERS 31 INFANTS					
	TOTAL	PER-CENTAGE	TOTAL	PER-CENTAGE	TOTAL	PER-CENTAGE	TOTAL	PER-CENTAGE	TOTAL	PER-CENTAGE	TOTAL	PER-CENTAGE
Normal living infants	16	26.2	10	58.8	29	78.4	26	83.9	76	93.8	30	93.8
Syphilitic living infants	21	34.4	3	17.6	5	13.5	3	9.7	2	2.5	—	—
Neonatal deaths	4	6.6	1	6.0	—	—	1	3.2	1	1.2	—	—
Stillbirths	11	18.0	3	17.6	1	2.7	1	3.2	2	2.5	—	—
Premature infants	4	8.2	—	—	2	5.4	—	—	—	—	2	6.2
Miscarriage	5	6.6	—	—	—	—	—	—	—	—	—	—
Total	61	100.0	17	100.0	37	100.0	31	100.0	81	100.0	32	100.0

three infants were born with the cord around the neck, one mother was in labor five days before admission to the hospital and one had a prolapsed cord for two days before admission. It is accordingly improbable that syphilis contributed to the abnormally high stillbirth rate. Late syphilis even with small amounts of arsenic and bismuth treatment gave relatively small risk to the unborn child.

An additional 22 mothers with congenital syphilis gave birth to 23 normal living infants. They had received varying amounts of routine therapy either before or/and during pregnancy. Congenital syphilis is almost never passed on to the next generation.

Penicillin During Pregnancy

Of the group of 281 syphilitic women treated with penicillin during pregnancy, 18 had early syphilis with open surface lesions, either primary or secondary. In the majority of these *Spirochaeta pallida* were demonstrated by dark-field examination. One hundred sixty-one cases were diagnosed as early latent syphilis, while 88 patients had late syphilis. There were 14 patients in whom a diagnosis of congenital syphilis was established. These have been omitted from the further analysis inasmuch as all delivered normal living infants, and inasmuch as it is well known that in this type of case therapy during pregnancy is of value only as it affects maternal syphilis. Infection of the fetus is extremely improbable even without treatment. Because of the relatively small number (18) of patients with open infectious lesions of syphilis we have, in Table III, combined infectious syphilis with early latent syphilis. Two of the three syphilitic infants, however, occured in the group of mothers having active secondary syphilis when placed under treatment with penicillin.

There were 71 syphilitic pregnant women observed by us who had had penicillin prior to pregnancy and who were given no additional antisyphilitic therapy. One patient in this group was treated for dark-field positive secondary syphilis Jan. 21, 1947, and delivered a normal living infant on Oct. 24, 1947. The remaining 65 mothers in this category in Table III had diagnoses of early latent syphilis when they registered in the prenatal syphilis clinic. This group also includes five mothers with late syphilis (see Table IV) and three with congenital syphilis. The latter three were left out of the table for the reason stated above. All three delivered normal living full-term infants.

TABLE III. OUTCOME WHEN PENICILLIN WAS GIVEN FOR EARLY SYPHILIS EITHER BEFORE OR
DURING PREGNANCY IN SYPHILITIC DELIVERIES AT THE PHILADELPHIA GENERAL
HOSPITAL FROM SEPTEMBER, 1946, TO MARCH, 1948, INCLUSIVE

	TREATMENT STATUS					
	UNTREATED		PENICILLIN DURING PREGNANCY		NO TREATMENT DURING PREGNANCY, ADEQUATE PENICILLIN THERAPY PRIOR TO CONCEPTION	
	60 MOTHERS 61 INFANTS		179 MOTHERS 181 INFANTS		66 MOTHERS 67 INFANTS	
OUTCOME OF PREGNANCY	TOTAL	PERCENTAGE	TOTAL	PERCENTAGE	TOTAL	PERCENTAGE
Normal living infants	16	26.2	171	94.5	63	94.0
Syphilitic living infants	21	34.4	3	1.7	1	1.5
Neonatal deaths	4	6.6	2	1.1	2	3.0
Stillbirths	11	18.0	2	1.1	1	1.5
Premature infants	4	8.2	2	1.1	—	—
Miscarriages	5	6.6	1	0.5	—	—
Total	61	100.0	181	100.0	67	100.0

TABLE IV. OUTCOME FOLLOWING PENICILLIN THERAPY FOR LATE SYPHILIS EITHER BEFORE OR
DURING PREGNANCY AT THE PHILADELPHIA GENERAL HOSPITAL, SEPTEMBER, 1946,
TO MARCH, 1948, INCLUSIVE

	TREATMENT STATUS					
	UNTREATED		PENICILLIN DURING PREGNANCY		NO TREATMENT DURING PREGNANCY ADEQUATE PENICILLIN THERAPY PRIOR TO CONCEPTION	
	12 MOTHERS 13 INFANTS		88 MOTHERS 90 INFANTS		5 MOTHERS 6 INFANTS	
OUTCOME OF PREGNANCY	TOTAL	PERCENTAGE	TOTAL	PERCENTAGE	TOTAL	PERCENTAGE
Normal living infants	13	92.9	88	97.8	5	83.3
Syphilitic living infants	—	—	—	—	–	—
Neonatal deaths	—	—	2	2.2	–	—
Stillbirths	1	7.1	—	—	–	—
Premature infants	—	—	—	—	–	—
Miscarriages	—	—	—	—	1	16.7
Total	14	100.0	90	100.0	6	100.0

Results

In analyzing the results obtained with penicillin therapy of the syphilitic pregnant women we have taken into account the amount of previous routine (arsenical and bismuth) therapy which they had received. Our results are in agreement with the recent study by Goodwin and Farber[3] in which they found no syphilitic infants of syphilitic mothers untreated during pregnancy provided: ''the mother has previously received 4.0 Gm. or more of arsphenamine (or its arsenical equivalent) together with concomitant bismuth; or 2.4 or more million units of penicillin . . . ; and whether this previous treatment was administered during a previous pregnancy or during a nonpregnant interval; and that the mother shows no clinical signs of active syphilitic infection; and that the mother is seronegative . . . or, if still seropositive, in low titer only (1 to 8 dilution units).'' As has been noted in a discussion of the patients treated with arsenicals and bismuth alone, there was no statistical significance between patients who had received little or no treatment prior to pregnancy and those who had adequate treatment before pregnancy, provided treatment was adequate during pregnancy. We, therefore, in Table III have not signified the amounts of previous ''routine'' therapy. Actually, only 19 mothers with early syphilis had received adequate antisyphilitic ''routine'' therapy prior to the pregnancy in which they received penicillin. One hundred seventy-nine mothers treated with penicillin (2.4 million units) during pregnancy gave birth to 181 infants (2 sets of twins). There were three syphilitic infants (1.7 per cent) in this group. Detailed case reports of these three failures follow:

CASE 1.—E. D. (D2), a 19-year-old Negro woman with early latent syphilis, reported to the maternity clinic in the fourth month of pregnancy. She had received approximately six injections each of an arsenical and a bismuth preparation at another institution very irregularly over the last year. Penicillin therapy with 2.4 million units in 7½ days was completed on Oct. 30, 1946. Her initial Kahn titer of 32 units was unchanged at delivery on March 18, 1947. She had been uncooperative and not seen at monthly intervals as requested. She was eventually retreated 335 days post penicillin at which time the Kahn titer was still 32 units. The infant was malnourished, weighed 6 pounds, 10 ounces at birth, and was placed on penicillin therapy for early congenital syphilis at 13 weeks of age, a definite diagnosis having been established by roentgenogram of the long bones showing early congenital osseous syphilis and a persistently high and rising titer in the infant's blood which reached 256 Kahn units before treatment was commenced.

CASE 2.—B. C. (D64), a 21-year-old Negro woman with dark-field positive secondary syphilis, was first seen in the eighteenth week of pregnancy. She completed treatment with 2.4 million units of penicillin in 7½ days on Jan. 10, 1947. She sustained an infectious relapse on April 30, 1947, but was uncooperative and was not readmitted for further therapy until two days before delivery on May 30, 1947. She therefore received only 12 doses, or 480,000 units, of penicillin before she delivered a 5 pound, 15 ounce infant. The child developed dark-field positive papular lesions at the age of 14 weeks when the Kahn titer was 128 units.

CASE 3.—A. S. (D172), a 25-year-old Negro woman with dark-field positive secondary syphilis, reported in the twentieth week of pregnancy, and completed therapy with 2.4 million units of penicillin on April 22, 1947. She had shown a satisfactory serologic response to penicillin in that her Kline test was 16 units on April 30, 1947, 3 units on May 31, 1947, 2 units on June 18, 1947, 1 unit on July 17, 1947, and less than 1 unit on August 13, 1947. On June 18, July 17, and August 13, the Kahn was negative though the qualitative Kolmer was strongly positive. The infant was placed on penicillin therapy at 10 weeks of age at which time the x-ray of the long bones showed evidence of congenital syphilis and the Kahn titer was 512 units. The mother sustained a serologic relapse with a high titer and was re-treated with penicillin eight months after delivery.

Probably syphilitic infection of the fetus in the first two cases just cited could have been controlled by re-treatment with penicillin in the last month of pregnancy had this been possible. In Case 3, on the other hand, the serologic response was such that there was no indication for further treatment during pregnancy. Our failure rate, nonetheless, compares very favorably with the published data to date. Ingraham[2] has compiled the statistics to the time of publication of his most recent paper.

The number of reported syphilitic pregnant women treated by various penicillin schedules aggregated 609, to which number some of those contained among the 149 in the publication by Tucker[4] should be added. The failure rate in terms of living syphilitic infants in these combined reports is 2 per cent.

Penicillin Prior to Conception

Sixty-six mothers treated with penicillin for early syphilis prior to becoming pregnant delivered 67 infants (1 set of twins) (Table III). The majority of these patients were under medical supervision from the start at the Philadelphia General Hospital, but a few had been treated elsewhere so that the dose of penicillin varied more in this group than in the previous one. Three patients had received as little as 1.2 million units aqueous penicillin for syphilis prior to the pregnancy observed by us. All were seronegative and delivered normal living infants. Three had received aqueous penicillin in dosage varying from 1.2 million to 2.8 million units plus 60 to 300 mg. arsenical and 200 mg. of bismuth. One received 3.6 million and one 3.2 million units aqueous penicillin. There were no failures in these eight patients. The remainder of the patients had received prior to their pregnancies the standard course of 60 injections of penicillin of 40,000 units each, totaling 2.4 million units as for the pregnant women previously described. There was one living syphilitic infant in this group. The case record follows:

CASE 4.—C. P. G. (D390), a 21-year-old Negro woman with early latent syphilis was first seen during the twenty-fifth week of pregnancy. She had received 2.4 million units of penicillin from Feb. 24, 1947, to March 4, 1947. When first seen in the maternity clinic (Dec. 17, 1947) she had a Kahn titer of 2 units. On Feb. 18, 1948, she sustained a serologic relapse at which time the Kahn titer was 256 units. She failed to return for re-treatment until the infant was born on March 31, 1948, at which time she was re-treated with 2.4 million

units penicillin in 7½ days. One year later her blood serologic test still showed 8 Kahn units. The diagnosis of early congenital syphilis was made in the infant at 6 weeks of age on the basis of a roentgenogram of the long bones showing changes characteristic of early congenital osseous syphilis and a titered blood serologic test of 256 units.

In addition there was one stillborn infant with a diagnosis of syphilis on the basis of a roentgenogram of the long bones on post-mortem examination which showed osteochondritic and periosteal changes of the inflammatory type. The mother in this instance (L. B. J., D346) was a 27-year-old Negro woman who had been treated for early latent syphilis with 2.4 million units penicillin in a previous pregnancy. At that time she delivered a normal infant 13 days post penicillin. The mother was temporarily lost from observation after April 9, 1947 (at which time Kahn titer was 1 unit). She delivered her second infant on Feb. 22, 1948, 400 days after she completed her penicillin therapy. This was a mascerated stillborn fetus weighing 4 pounds, 5 ounces. At delivery her blood serologic test was positive and the Kahn titer was 32 units. Both of these failures could have been prevented by adequate medical follow-up and cooperation of the mother during pregnancy and re-treatment care for the treatment failure from previous therapy. These results are similar to those obtained by Ingraham and associates,[5] Speiser and associates,[6] and Tucker.[7]

A study of Table III will indicate that there were ten unfavorable outcomes among the pregnant syphilitic women treated with penicillin either before or during pregnancy. There were ten disasters in these two categories. These consisted of four neonatal deaths, three stillbirths, two premature infants, and one miscarriage. The percentages in aggregate or individually are as low or lower than those normally expected in nonsyphilitic deliveries as shown in Table I.

Five patients who had received penicillin prior to pregnancy were re-treated with penicillin during pregnancy. One was originally treated for secondary syphilis 281 days before delivery. She sustained a serorelapse and penicillin therapy was begun six days before she delivered, by which time she had received 1,920,000 units of aqueous penicillin. She delivered a normal infant who was seropositive (Kahn titer 128 units) at birth, but whose blood serologic test for syphilis became negative by 3 weeks and remained negative. Another mother with early latent syphilis received penicillin 794 days before delivery. She completed a second course of penicillin seven days before delivery, because of failure of the blood serologic titer to drop appreciably. Her infant remained seronegative.

A patient originally treated for early latent syphilis 365 days before delivery was seronegative during pregnancy but received penicillin on the obstetrical ward due to a kidney complication. She completed 2.4 million units aqueous penicillin six days before being delivered by cesarean operation of a one-pound dead infant. This fetal death could not be attributed to syphilis.

A white woman originally treated at another institution for secondary syphilis 326 days before delivery registered in the prenatal clinic in the thirty-first week of pregnancy. Her Kline serologic titer was 256 units. She had had no follow-up since her original course of penicillin. She was re-treated with 4.8 million units of penicillin in oil and beeswax and was delivered, 30 days after completing therapy, of a normal living infant.

The fifth mother originally treated with penicillin for secondary syphilis on Dec. 3, 1946, developed relapsing secondary syphilis during pregnancy and was retreated June 3, 1947, with 2.4 million units aqueous penicillin. At delivery on Sept. 13, 1947, she had 8 Kahn units. The infant was normal.

An additional mother received a second course of penicillin during pregnancy. She was a 25-year-old Negro woman originally treated in another city during the fourth month of pregnancy. The dose of penicillin could not be ascertained. Inasmuch as she showed a Kahn titer of 32 units in the thirty-second week of pregnancy she received an additional 2.4 million units of penicillin. She delivered a normal nonsyphilitic infant.

The infants in Table III, similarly to those in Tables II and IV, were followed, if possible, for twelve months or more. Two hundred thirty-four infants in this group were born alive and apparently free of syphilis. Seventy per cent of these infants were observed for 2 months or more after delivery, while 50 per cent were followed from 6 to 12 months.

Table IV illustrates the outcome of late syphilis in pregnancy treated with penicillin either during or prior to pregnancy. Inasmuch as there were no syphilitic infants in this category no explanation of the results is necessary. Seventy-two per cent of the infants in this group were followed for more than 2 months while 42 per cent were followed from 6 to 12 months.

Summary and Discussion

The clinical controls in this study show that the likelihood of a normal full-term infant in the type of material in which we are dealing is about 88 per cent. If infectious syphilis of short duration enters the picture there is no chance of obtaining a normal healthy infant when the disease is in the primary or secondary stage. There is some possibility of obtaining a healthy infant, in actuality about a 30 per cent chance, if the expectant mother has untreated early latent syphilis. In the late stages of the disease there is virtually no possibility of a syphilitic infant resulting irrespective of therapy. Among fourteen untreated pregnancies in women with late syphilis there were no living syphilitic infants. Among 180 pregnancies in women with late syphilis treated with varying amounts of arsenic and bismuth, no living syphilitic infants resulted, and the same was true for the expectant mothers with late syphilis treated with penicillin.

The disastrous effects of syphilis on the fetus are accordingly to be found early in the course of the disease and in the late stages can be effectively controlled with relatively small amounts of antisyphilitic therapy. It is well known from our own experience and that of others that women with syphilis of five or ten years' duration or even more may occasionally give birth to a syphilitic infant if their infection is still active and uncontrolled during the pregnancy. A constant vigilance is accordingly necessary and treatment should always be given in subsequent pregnancies if there is any reasonable doubt as to the activity of the infection in the mother. Nonetheless, in the present study, either without treatment or with varying amounts of arsenic and bismuth or penicillin either before or during pregnancy, the women with late syphilis averaged 90.4 per cent normal full-term living infants among 290 pregnancies which is better than for the control group (87.6 per cent).

Where arsenic and bismuth were used in pregnant women with early syphilis, failures were most likely to result when no treatment was given during the pregnancy, but here again even a small amount of treatment given prior to conception was able to improve the outcome considerably and resulted in 59 per cent normal full-term living infants. "Adequate" treatment in late pregnancy with no antecedent therapy occasionally resulted in treatment failure when the mother developed surface infectious lesions before the treatment

was commenced. It may be assumed in such instances that the fetus was already infected in utero before medical care was instituted and that treatment during pregnancy was ineffective in curing the already infected fetus.

With the arsenical and bismuth cases, as with the penicillin cases, the most effective preventive treatment seems to be adequate preconceptional therapy. If the response is normal, little or no treatment during pregnancy seems to be essential. Under these circumstances only one living syphilitic infant resulted and one known syphilitic stillbirth among 95 pregnancies.

Provided the fetus is not already diseased beyond hope when treatment is started, the only failures from penicillin therapy seem to result when too much reliance is placed upon an individual course and medical posttreatment follow-up during the pregnancy is inadequate. Since penicillin readily permeates the placenta and will treat the already infected fetus in utero, disastrous outcome can usually be prevented, even with initial treatment failure by re-treatment just before term. A blood serologic test (titered if positive) is recommended once monthly during pregnancy in all women who have been known to have syphilis, irrespective of their previous therapy. Serologic and infectious relapses in the mother may thereby usually be detected in time to prevent the birth of a syphilitic child. A review of the several case reports in the text citing the treatment failures show the extreme degree of cooperation and vigilance which is necessary to prevent the occasional treatment failure. All penicillin treatment in this study has been given on hospitalized patients with aqueous solution and frequent dosage. It is felt that this type of handling of the syphilitic pregnant woman is desirable but not absolutely essential. When penicillin in absorption-delaying vehicles is used on either hospitalized or ambulatory patients it seems important that dosage be in such magnitude and with such frequency as will insure adequate blood and tissue levels not only in the mother but also in the fetus. To the best of our present knowledge this requires daily injection over a period of at least one week.

Suggested Management of Latent and Late Syphilis in Pregnancy

In a large prenatal syphilis clinic a number of practical problems in patient management arise that are not answered by a consideration of the previously untreated pregnant woman with infectious early syphilis with which most previous reports have been concerned. There is no substitute in the strict sense for an individual approach to each patient and a thorough knowledge of syphilology and obstetrics. Yet some treatment problems arise with sufficient frequency to make discussion possible. The following suggestions do not represent the only way of handling such situations, yet they have yielded the degree of success reported in this paper. We will not discuss the management of previously untreated symptomatic early syphilis in pregnancy which has been largely covered in other papers.

When the pregnant woman has latent syphilis of unknown duration, we have given a single course of penicillin treatment as early in the pregnancy as possible. The blood serologic response is ordinarily of little value in de-

termining the effectiveness of treatment in such a case since it will usually change very little by the time of delivery. There will be an indication for re-treatment before term in the occasional case in which there is an initial drop followed by an increase in the titered serologic test.

Many women will have had arsenical and bismuth therapy in varying amounts prior to pregnancy. Many of these women will still have positive blood serologic tests for syphilis and a few will be seronegative. In an occasional instance the disease will be known to be of long duration, the previous therapy adequate and the response to medical care normal. In such instances, as indicated in the statistics presented in this paper, it is satisfactory not to give treatment during the pregnancy. As a rule, however, we have given a course of penicillin therapy as outlined above to syphilitic expectant mothers who have not previously received this drug. Penicillin is employed routinely during pregnancy when previous arsenical and bismuth therapy has been inadequate, regardless of the duration (or stage) of the disease.

If the pregnant woman was treated for syphilis with penicillin and a written record of this treatment showed it to have been in satisfactory amount, according to accepted standards, then further specific treatment during pregnancy is withheld providing the response to antecedent treatment has been normal for the stage of the disease in question. When there is any uncertainty as to the amount of previous treatment or when the response has not been normal re-treatment during the pregnancy is uniformly carried out.

It is to be remarked that many women first treated in the latent or late stage of the disease will retain a persistently positive serologic test for syphilis for years. If previous treatment has been in accord with accepted standard and if the titer is low in the magnitude of 4 to 8 Kahn units, we are less concerned than if the titer is high. It has seemed to us best to treat uniformly during pregnancy all women with persistently high blood serologic titers of syphilis reagin.

The above discussion refers to women with acquired syphilis. If a diagnosis of congenital syphilis is established in the pregnant woman, the risk for the fetus is so small as to cause little concern. If the woman has had no previous treatment she is given a single course of penicillin during pregnancy with the idea that it may benefit her and possibly avert the development of late symptoms such as interstitial keratitis. Even with this symptom, if the eye lesion has not developed by the time the woman reaches the child-bearing age, the risk that it will subsequently occur is small. If the patient with congenital syphilis has had any type of satisfactory treatment before pregnancy we do not re-treat her during the pregnancy.

It is emphasized that there is no substitute for the individualized approach for each patient with latent or late syphilis, especially when antecedent therapy has been given. Yet the foregoing discussion will show the type of thinking on which decision as to treatment was reached in the present study.

Conclusions

1. This report concerns 820 pregnancies of syphilitic women observed at the Philadelphia General Hospital between Jan. 1, 1945, and March 31, 1948, and a control group of 5,596 nonsyphilitic pregnancies. Their distribution by type of treatment is illustrated in Table V.

TABLE V. DISTRIBUTION BY TYPE OF TREATMENT OF THE 820 PREGNANT WOMEN STUDIED AT THE PHILADELPHIA GENERAL HOSPITAL

TYPE OF TREATMENT	TOTAL MOTHERS	PERCENTAGE	TOTAL INFANTS	PERCENTAGE
Untreated.—				
Primary-secondary	7	0.9	7	0.9
Early latent	54	6.6	54	6.4
Late	14	1.7	14	1.7
Subtotal	75	9.2	75	9.0
Arsenical-Bismuth.—				
Before and During:				
Primary-secondary	10	1.2	10	1.2
Early latent	184	22.4	188	22.5
Late	174	21.3	180	21.5
Congenital	22	2.7	23	2.7
Subtotal	390	47.6	401	47.9
Penicillin.—				
During:				
Primary-secondary	18	2.2	18	2.1
Early latent	161	19.6	163	19.5
Late	88	10.7	90	10.8
Congenital	14	1.7	14	1.7
Subtotal	281	34.2	285	34.1
Before:				
Secondary	1	0.1	1	0.1
Early latent	65	7.9	66	7.9
Late	5	0.6	6	0.7
Congenital	3	0.4	3	0.3
Subtotal	74	9.0	76	9.0
Total	820	100.0	837	100.0

2. The outcome of pregnancy is compared in three groups each of early and late syphilis as follows: 75 pregnant women whose syphilis was untreated; 462 women treated with arsenic and bismuth before or during pregnancy; 344 women treated with penicillin either before or during pregnancy.

3. With late syphilis in pregnancy no treatment or a small amount of either arsenical and bismuth or penicillin was found to reduce the number of living syphilitic births to zero, and the number of normal full-term births to a figure higher than that of the nonsyphilitic control group.

4. The problem of treating the syphilitic pregnant woman to prevent the infection of the fetus resolves itself largely, therefore, to the adequate treatment of early syphilis and to satisfactory medical follow-up to detect treatment failures.

5. When "adequate" arsenical and bismuth therapy was employed before or during pregnancy or both, 93.8 per cent normal full-term infants resulted and 2 per cent living syphilitic infants.

6. When penicillin was employed either before or during pregnancy 94.5 per cent normal full-term infants resulted and 1.7 per cent living syphilitic infants.

7. In this study aqueous penicillin (crystalline G) was employed in total dosage of 2.4 million oxford units over a period of 7½ days in 60 injections of 40,000 units each. Because of its ease of administration and effectiveness it should replace completely arsenical and bismuth treatment.

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THE STRUCTURE AND FUNCTION OF THE CORTEX
OF THE HUMAN OVARY*

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I N A paper read before the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, we[1] presented an investigation concerning ovogenesis in the adult human ovary. Swezy and Evans,[2] in 1931, showed conclusively that the estrous cycle and follicular cycle in certain animals had a definite related rhythm; and that, in the adult animal, ovogenesis continued. They described the germinal epithelium as markedly proliferative. This in turn invaded the cortex and developed new follicles. They presented some fragmentary evidence that this was also true in the human being. Simkins,[3] a year later, emphasized the reduction of primary follicles in the human ovary, and pointed out that this took place rather strikingly before and even after puberty. He contended that the germinal epithelium did not become active or produce new ova after birth. He stated, however, that the ovogenesis that occurred came directly from the cortical tissue. In our study we clearly demonstrated the activity of the germinal epithelium and its ability to produce new ova as the germinal cells penetrated deeper into the cortex. We felt, however, that the suggestion of Simkins was quite plausible. This we were not able to prove, because with the penetration of the germinal epithelium into the cortical tissue, it was most difficult to differentiate the character of the cells. Since our presentation we have noted the appearance of primordial follicles deep in the cortical structure near the large blood vessels, and are inclined to believe that both sources may share responsibility in this new ovogenesis. Swezy and Evans also tried to fit the follicular cycle into the menstrual cycle, and they felt there were definite variations. We made similar observations, but felt this relationship was more constant than Swezy and Evans had given us to believe. This coincides with the views expressed by Schröder[4] in 1928. In looking over these ovaries we were impressed with certain characteristic features in the cortex, and this paper will deal especially with this structure in the human ovary.

We had noted in the human ovary of the embryo of 24 weeks, that the structure was made up practically entirely of primordial follicles, penetrating germinal epithelium, and a very tiny loose central structure which contained the blood vessels. No cortex was demonstrable. In the ovary of a child of 10 months of age the egg-bearing area was the most superficial. The tissue of the deeper medulla was made up of markedly hypertrophic and hyperplastic blood vessels, and a very considerable amount of smooth muscle moving upward and

blending gradually into a small but well-differentiated cortex. The egg-bearing area was devoid of this tissue. We concluded that the source of this developing cortex was the smooth-muscle cells of the media of the blood vessels. The differential staining with van Gieson gave it all a similar deep yellow color consistent with that of smooth muscle elsewhere. In reviewing the sections from an ovary of a child 30 months of age, the cortex was better developed and sent fingerlike processes into the egg-bearing area. The blood vessels in the medulla

Fig. 1.
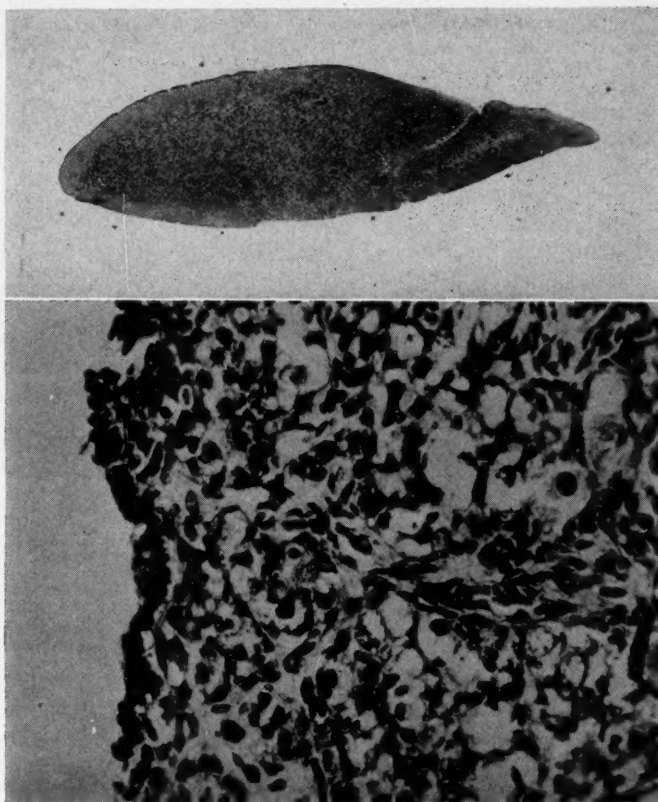
Fig. 2.

Fig. 1.—Ovary, 24-week fetus. Whole ovary made up entirely of germinal epithelium, its proliferation, and primordial follicles. Small medulla carrying blood vessels in loose connective tissue seen in the left middle portion of the picture (light area). (Hematoxylin and eosin.)

Fig. 2.—Ovary, 24-week fetus. Showing active germinal epithelium with its invading cells in close connection with the many ova.

were likewise markedly hyperplastic and embedded in a loose connective tissue with strands of definite cortexlike tissue intermingled, the latter being in close association and actually originating from the blood vessels. The cortex has increased considerably at 11 or 12 years of age, but by no means to its fullest extent. The cortex approached the more adult type by 15 years of age, and by 19 years of age was well developed. To investigate this phase of development we have set aside thirty-five human ovaries ranging from birth to 18 years of age, with some fifteen ovaries being between birth and 5 years of age, or the time

during which the most striking changes take place. Schwarz and Saxton are now preparing to study this material, and will report in detail concerning this interesting observation.

One of us (O. H. S.) has long observed that when the cortex was stained with the van Gieson stain, it appeared similar to smooth muscle. We called attention to this fact in a previous paper,[1] and for want of a better term, referred to the cortex as a hybrid structure. The generally accepted characteristic of
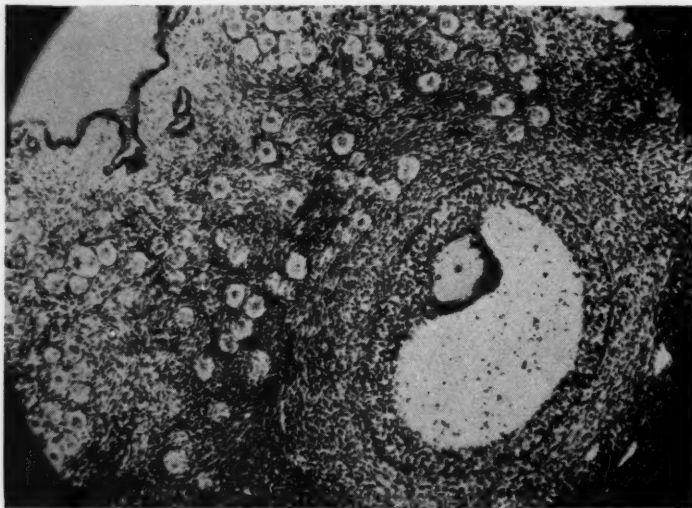

Fig. 3.—Ovary, 2 years old, low power. Showing primordial follicles entering into the deeper structure. Note developing follicle in lower portion of picture with well-developed theca-interna cells. Note the dense cortex between the follicles in the deeper area, and how it is infiltrating the upper portion of the ovary.

the cortex can be best and most concisely presented by quoting directly from Novak's[5] textbook, *Gynecological and Obstetrical Pathology*. He states, ''The ovary is divisible into the cortex and the medulla. During reproductive life the former is broad, constituting from one-half to two-thirds of the depth of the ovary. It consists of a very characteristic stroma in which are found the follicular elements of the ovary. The stroma is made up of spindle-celled connective tissue cells placed very compactly. There is only slight superficial condensation of this connective tissue into a layer called the tunica albuginea, which is much less marked in the male gonad. Only a few involuntary muscle fibers are found, chiefly around the larger blood vessels.'' He describes further, ''The theca interna is a highly vascular layer of connective tissue cells which surround the granulosa cells of the follicles, the theca interna cells being the source of nourishment for the granulosa cells in which there are no blood vessels.'' He states that the cells of the theca interna are definitely connective tissue type, although, as he will describe later, they are very sensitive to hormonal influences which at various phases give them an epithelioid appearance. These are known as the theca lutein cells. He further states that external to the theca interna is a layer of rather condensed ovarian stroma, the theca externa, which so far as he knows plays no part in the characteristic life history of the follicle. Concerning fibromas of the ovary, we again are quoting directly from Novak, ''The fibroma is made up of connective tissue of varying histological appearance, even in different parts of the same tumor. In some tumors the fibrous tissue is very light-textured, with small fusiform or stellate cells and with an abundance of

intercellular substance. The nuclei are rather small and fusiform, so that such areas may resemble keloid tissue in appearance. Perhaps more frequently the fibrous tissue is more cellular, the individual cells being often spindle shaped, rather compactly placed, and arranged in individual bundles, so that they may even resemble involuntary muscle. As a matter of fact, muscle bundles may be demonstrable in some tumors, which therefore are designated fibromyomata.''
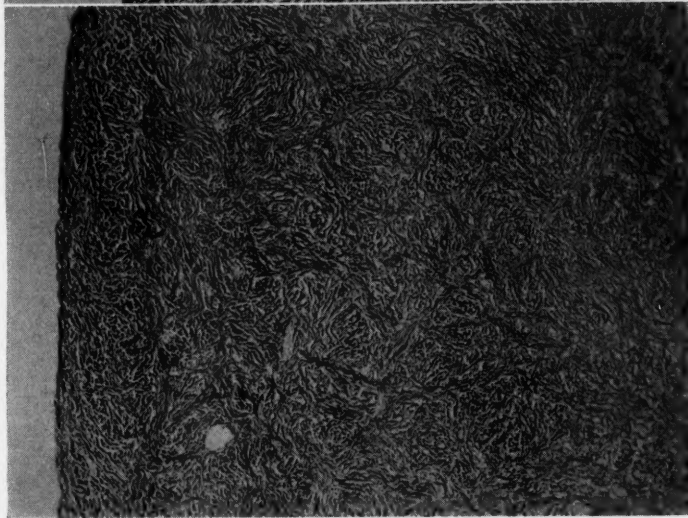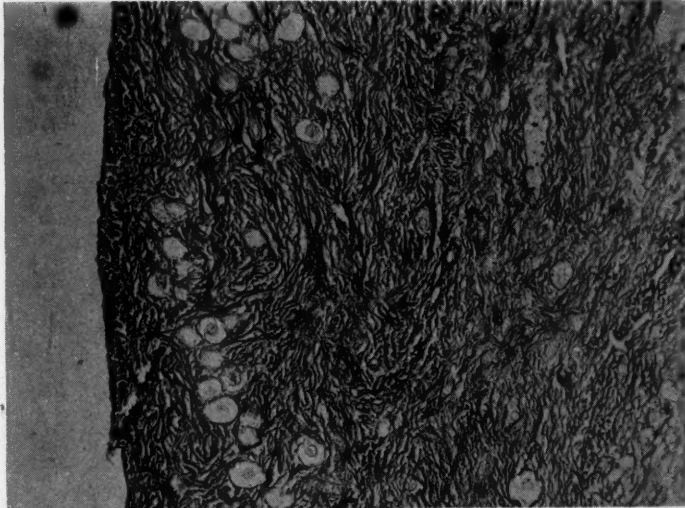
Fig. 4.

Fig. 5.

Fig. 4.—Ovary 19 years old. Well-developed tunica and cortex. Note scarcity of ova even at this age. Well-developed cortex which is more dense in lower right. (Hematoxylin and eosin.)

Fig. 5.—Ovary, 19 years old. Black areas show sprinkling of connective tissue (actually red), most striking in small area at left just below surface. Remaining cortex stains predominantly light as does smooth muscle (actually yellow). Black and white print of van Gieson stain.

In view of these rather striking observations, we consulted several recent texts on embryology, but no particular light was thrown on the subject as their descriptions were rather vague. Arey[6] and Patten[7] were among those consulted. We then turned to the more elaborate monograph of Keibel-Mall[8] written in
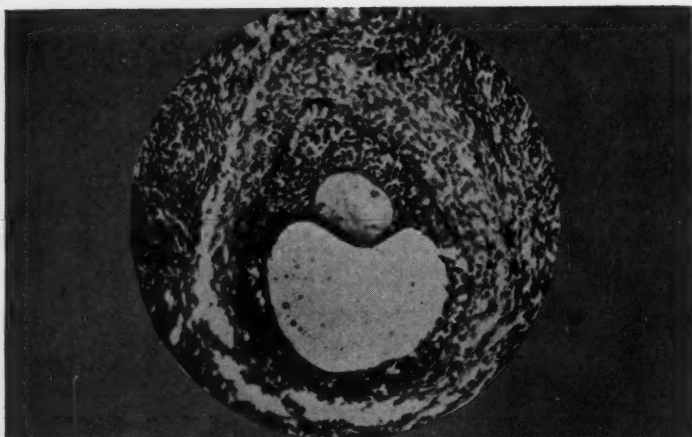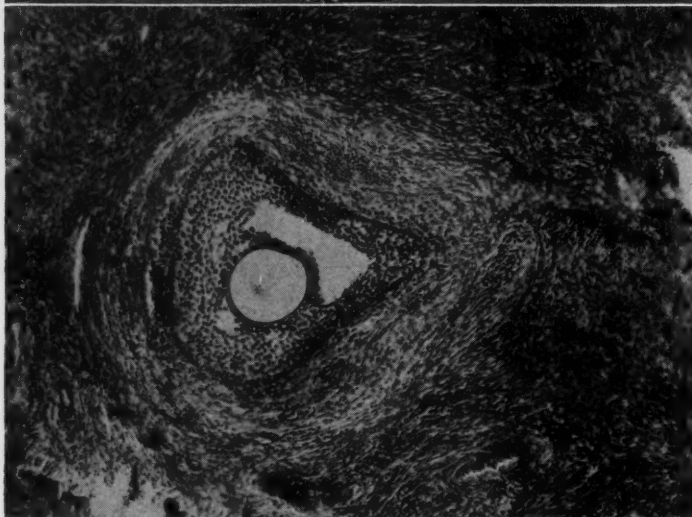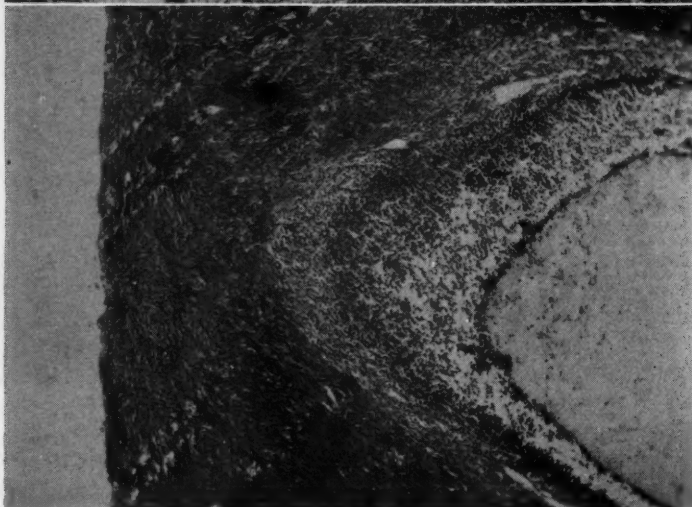
Fig. 6.

Fig. 7.

Fig. 8.

Fig. 6.—Ovary, theca cone. Note increased theca-interna cells on right with pull on granulosa. Theca interna closely associated with flattened cells of theca externa seen best in lower right portion of picture. This, according to Strassmann, effects a pull which brings the developing follicle closer to the surface of the ovary. Strassmann's picture.

Fig. 7.—Ovary, human. Theca cone almost identical to Fig. 6. (Hematoxylin and eosin.) Original picture.

Fig. 8.—Ovary, human. Theca cone of a larger follicle approaching the surface of the ovary. Original picture.

1912. Here also the information was very meager. They definitely state that they do not know for a certainty the origin of the cortex. We quote directly from the monograph: "whence this young cortical zone comes, we cannot say with certainty. There are, however, two possibilities which may act singly or together. On one hand, the different or genitaloid cells of the cortical zone of the epithelial nucleus divide, and thus, notwithstanding the progressive transformation of the cells of the nucleus into young ova, a new neogenic cortical zone may continually reform. In favor of this mode of development are mitotic figures and the gradual transition of the cortical zone of the epithelial nucleus
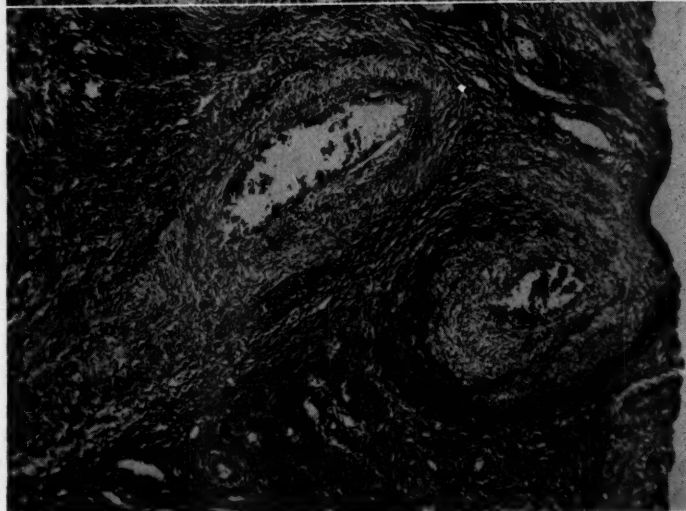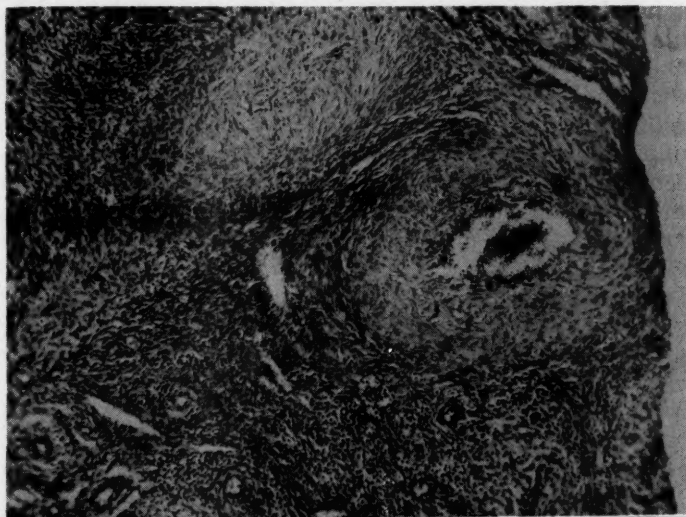
Fig. 9.

Fig. 10.

Fig. 9.—Ovary, adult, upper cortex. Two good-sized vessels artery below and vein above, showing slight hyaline change with marked nuclear activity. Adventitia not perceptible, but note the close association of the outer media with the surrounding cortical stroma. Also note the similar staining intensity. (Hematoxylin and eosin.)

Fig. 10.—Ovary, adult, upper cortex, same field as in Fig. 9. Note the slight circular amount of elastic tissue at the periphery. Also the slight hyaline change in the wall and the absence of the adventitia, the vessel wall blending directly with the cortex. Note the disturbed internal elastic membrane: the absence of the adventitia with direct blending of the media with the adjacent stroma. (Orcein-van Gieson.)

in a neogenic zone. The second theory is that the superficial epithelium alone forms the neogenic zone.'' In our opinion, these statements need much clarification, and give little information.

We will report briefly, in addition to this paper, some recent observations on the structure and possible origin of the so-called fibromas. Woolsey and Schwarz are preparing a detailed study of these tumors. Schwarz has recently observed in the pregnant uterus that both arteries and veins undergo a marked hyperplasia of their walls. This hyperplastic tissue invades the adjacent musculature. Schwarz and Hawker are reviewing these findings in a large series of pregnant uteri at various stages of gestation. Likewise, the vessels of the ovary in the vicinity of the hilus undergo a similar hypertrophy and hyperplasia. This has been observed in the ovaries which contain a corpus luteum of late vascularization or early maturity. Recently, Giorgi[9] (1948) studied a series of ovaries in regard to this hyperplasia during pregnancy. The illustrations chiefly concerned the arteries, which were markedly hypertrophic and hyperplastic; but he called attention to the ''buckling-in'' of these cells into the lumen of the artery, with a very beautiful picture of a hyperplastic vein. In discussing the character of the veins, Giorgi describes enlarged veins in the ovaries of pregnancy at term which ''buckled-in'' just like those of the arteries. Giorgi calls attention to the marked hyperplasia of the vein media with the thinning of the walls in various places, and the extension of the tissue into the adjacent surroundings, which in the medulla and hilus is actually smooth-muscle tissue. He notes the blending of the vein wall with this tissue and also stresses the absence of the adventitia. He attaches no great significance to this as to the possible origin of the cortex. He mentions that this tissue may function as erectile tissue, which in some manner may help to bring the developing ova to the surface. In our observations on the cortex of the ovary we found that, in general. when the cortex went deeper into the ovary the staining with hematoxylin and eosin was usually more intense. In using the van Gieson stain, it was found that the deepest color of yellow was produced in the area where the deepest hematoxylin staining took place. From these observations we felt that the structure of the cortex as a whole could be regarded as tissue similar to that of smooth muscle. Another interesting feature was the character of the blood vessels in this deeply staining cortex. The media of the vessels, both arteries and veins, and more especially the veins, showed a most intimate relationship to the cortical stroma. In fact, a very common observation was that these vessels carried with them no adventitia whatsoever, or at most only a meager one. The close relationship between the theca interna and theca externa cells was very striking. In the celloidin sections that we observed, this was very definite indeed. In paraffin sections there is not infrequently seen a slight pulling-away of the theca interna which must be regarded as due either to shrinkage or to heat distortion in the paraffin embedding. It is interesting to note that the deeper staining the cortical tissue with hematoxylin, the more it stains yellow with van Gieson stain.

The cortex is the most persistent structure of the ovary. Ovaries of women between 45 and 50 years of age, who are still menstruating regularly, show little or no functioning follicular tissue in the cortex, although a corpus luteum develops. The cortex is active in appearance and continues so even after the menopause. One of our illustrations, from a woman 56 years of age and 7 years postmenopausal, shows a large low-power picture of the ovary in which there is a very well-developed and deeply staining cortex throughout the structure.

The next question arises therefore, as to the derivation of this smooth-muscle-like tissue. We feel that with a constant hyperplasia of both veins and arteries in the ovary, the media of the blood vessels must be considered a definite source. We thought that it would be of some interest to go over the sections of the so-
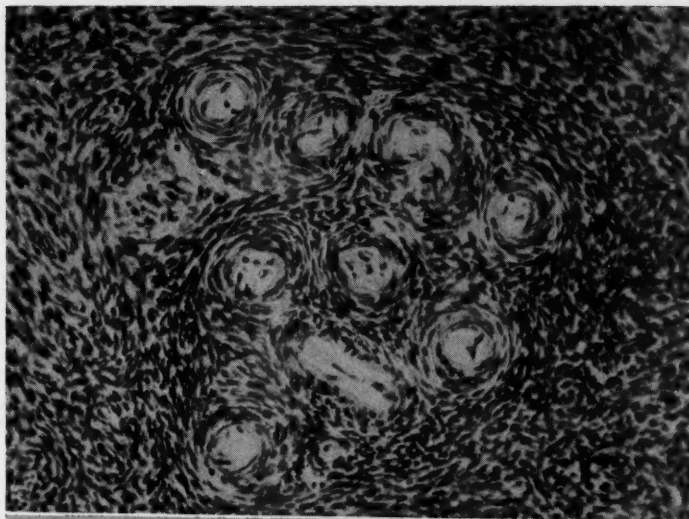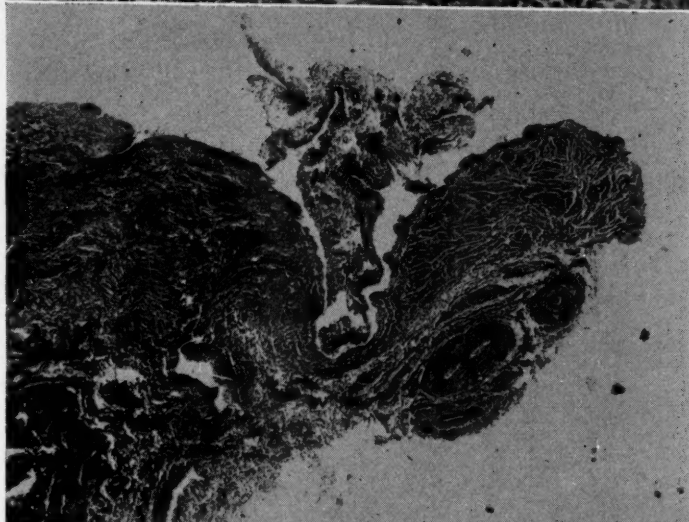
Fig. 11.

Fig. 12.
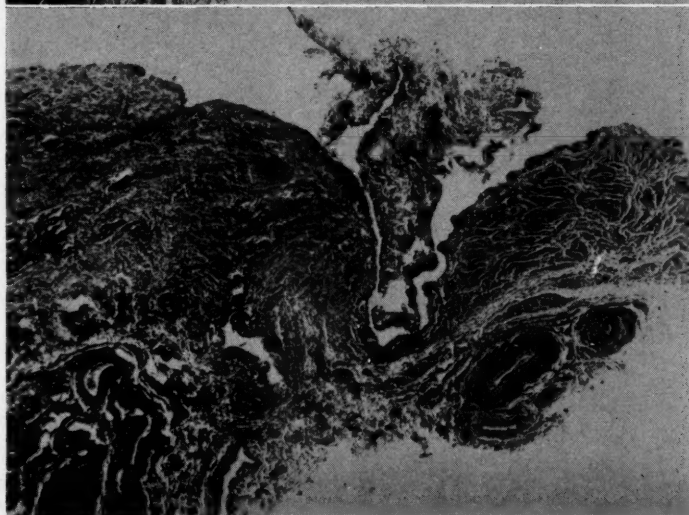
Fig. 13.

Fig. 11.—Ovary, adult, deep cortex. Showing the very nuclear activity of the arteries of small size, the media blending directly into the stroma and showing no apparent adventitia. (Hematoxylin and eosin.)

Fig. 12.—Ovary, 10-month-old child. Showing markedly hyperplastic vessels forming muscle tissue extending directly to the cortical region, with the cells becoming more compact, smaller, and fibrillary as the area of the upper cortex is reached. (Hematoxylin and eosin.)

Fig. 13.—Ovary, 10-month-old child. Orcein-van Gieson stain showing structure from the large vessels staining yellow (light in black and white pictures), and strikingly revealing the direct continuation from the deeper vessels.

called fibromas of the ovary that could be found in our files; and after reviewing some forty cases some very striking observations were made. These tumors stain chiefly yellow with the van Gieson stain. They undergo the characteristic hyaline degeneration just as do myomas of the uterus. Special staining frequently shows hyalinization, which of course stains red with van Gieson and green with the Masson stain, the muscle-tissue-like bundles standing out in bold relief. We feel that these fibromas appear more like myomas; and their origin seems to be definitely from the blood vessels.

Fig. 14.
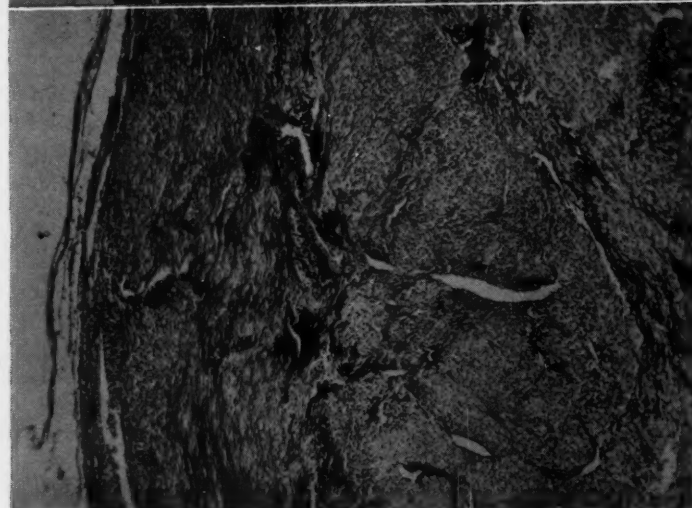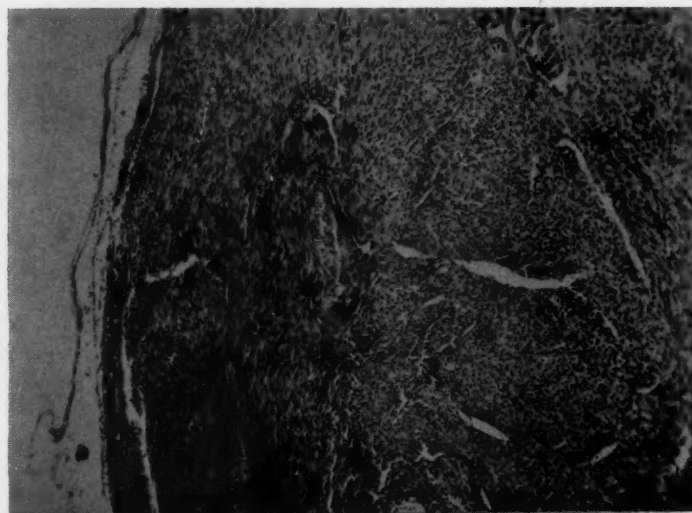
Fig. 15.

Fig 14.—Ovary, so-called fibroma, showing congested and compressed superficial cortex, with tumor at left center, resembling in appearance a myoma, and undergoing slight hyalinization. (Hematoxylin and eosin.)

Fig. 15.—Ovary, so-called fibroma, same field as Fig. 14. Light areas stain yellow with van Gieson like myomas, with connection tissue matrix and small hyaline areas appearing black, but actually staining red with van Gieson. Upper cortex to left shows more connective tissue and hyalinization (black). (Orcein-van Gieson stain, but black and white print.)

In 1940, Strassman[10] called attention to a peculiar structure in relation to the developing follicle which he called a "theca interna cone." This picture is developed by a marked hyperactivity of the theca-interna cells at the upper portion of the developing follicle; or that portion which is nearest the cortex. These cells with the aid of the closely approximated theca-externa cells pull the granulosa and follicle toward the surface of the ovary, the supposition being that this process raises the follicle to a position in the ovary where the ovulation can take place. Strassmann demonstrated these cones in the horse, cow, pig, and human being. He thinks that these structures have not been observed here-

Fig. 16.
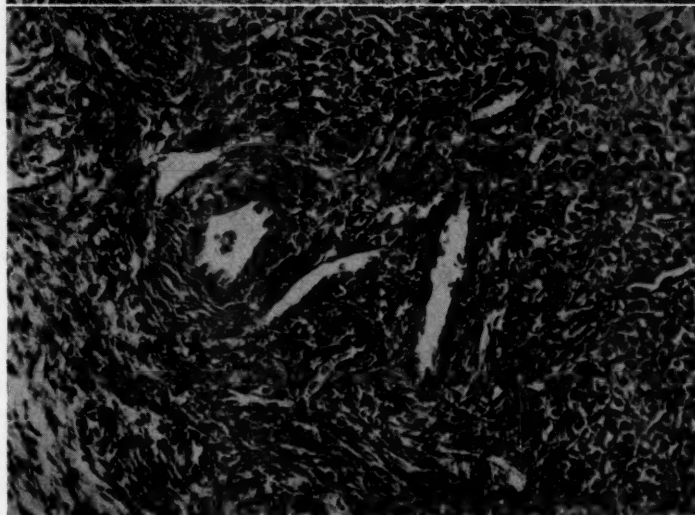
Fig. 17.

Fig. 16.—Ovary, so-called fibroma, very small in diameter (1.2 mm.), mid cortex. Note the numerous arteries and veins in the tumor, especially in the periphery, showing no adventitia and blending intimately with the tumor tissue. Slight hyaline change and liquefaction in the center. (Hematoxylin and eosin.)

Fig. 17.—Ovary, so-called fibroma, same field as Fig. 16, high power, showing an artery and three veins. Note the thickened artery between two veins, and its close association with the tumor structure. The veins have the same close relationship to the surrounding tissue. (Hematoxylin and eosin.)

tofore; that serial sections are necessary; and that the block must be taken perpendicular to the surface of the ovary. This may be true to demonstrate the cones constantly, but they can be frequently found in routine sections in which the block was casually taken through the proper area. It was quite easy to find well-developed cones, and we have included several illustrations. Unfortunately, Strassmann's work did not come to our attention until after the presentation of our paper on ovogenesis, or we could have commented on them at that time. Suffice it to say, that we consider Strassmann's observations as to the theca cone absolutely correct. The demonstration of the theca cones calls to our attention the large amount of theca-interna cells developing in the ovary constantly. It is generally accepted that they differentiate directly from the cortical cells, being closely associated with the cortical theca externa. With the great demand for these cells, the cortex must supply them. How then does the cortex assume this function? We propose that the media of the blood vessels, both arteries and veins, is the most logical source to be considered.

From the present observations concerning the cortex of the ovary, we assume that it develops from birth, and reaches its fullest extent around the twentieth year. It is almost entirely made up of tissue similar to that of smooth muscle, and has a very close relationship to the media of the blood vessels. This highly indicates that these structures may be the source of the developing cortex.

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FACE AND BROW PRESENTATION*

The Experience of the Johns Hopkins Hospital, 1896 to 1948

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THE subject of extended positions of the fetal head has been largely neglected in recent American literature, and many of the statistics in the standard obstetrical texts are in need of revision in the light of current thought and practice. Three excellent papers dealing with fairly large series of face presentation have appeared since 1943.[1, 2, 3] Little, however, has been written regarding brow presentation, since the large series of Fink[4] in 1925. Current statistical data concerning face presentation are based on approximately 300 patients and no recent data regarding brow presentation have appeared. It was felt worth while, therefore, to submit the face and brow experience of this clinic to statistical survey.

From the inception of the clinic in 1896 to Dec. 31, 1948, there were 141 face presentations and 45 brow presentations at the Johns Hopkins Hospital. These diagnoses of position were made on admission. There were in addition 16 instances of face presentation associated with grossly deformed fetuses. These have been omitted from the following statistical survey since they present a problem entirely different from that of the well-formed infant with an extended head. It has been the practice of other authors, when dealing with this subject, to include these abnormal infants in the general data and to correct for them in the fetal mortality studies.

TABLE I. FACE AND BROW PRESENTATION, INCIDENCE ACCORDING TO RACE, 1896-1948

	DELIVERIES	FACE	RATE	BROW	RATE	TOTAL	TOTAL RATE
White	33,222	61	1:652	28	1:1,187	89	1:373
Negro	32,708	80	1:409	16	1:2,044	96	1:340
Total	65,930	141	1:468	44	1:1,498	185	1:356

Table I shows the incidence of extended position by race in 65,930 deliveries. The incidence of face is 1 in 468 deliveries, while brow occurs once in 1,498 deliveries. The incidence of the former is slightly greater than 1 in 542 quoted by Rudolph, and 1 in 526 cited by Posner, but somewhat rarer than the figures of 1 in 300 appearing in current texts. The occurrence of brow presentation too is more rare in this series than is commonly cited in obstetrical texts. The predominance of face in the Negro and brow in the white, shown in Table I, is worthy of note but no explanation can be offered.

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*Read by invitation before the Brooklyn Gynecological Society on April 20, 1949.

TABLE II. FACE PRESENTATION, POSITION ACCORDING TO RACE

	WHITE		NEGRO		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Right mentum anterior	10	18.1	13	17.3	23	17.7
Left mentum anterior	13	23.6	19	25.3	32	24.6
Right mentum transverse	5	9.1	13	17.3	18	13.8
Left mentum transverse	9	16.4	9	12.0	18	13.8
Right mentum posterior	12	21.8	14	18.7	26	20.0
Left mentum posterior	6	10.9	7	9.3	13	10.0
Total anterior	23	41.8	32	42.7	55	42.3
Total transverse	14	25.5	22	29.3	36	27.7
Total posterior	18	32.7	21	28.0	39	30.0
Total	55		75		130	

The primary position for both face and brow are shown in Tables II and III. As far as face is concerned the anterior position of the chin predominates although this dominance is not as great as was found by Reddock or Posner. The figures in these tables are more in agreement with those of Rudolph. The statement that left mentum anterior and right mentum posterior occur with the greatest frequency seems to be borne out by these figures, but again, this is not as striking as has been previously cited. Of particular interest are the 39 cases of face presentation in which the primary position was mentum posterior. These represent 30 per cent of the term face deliveries in which the initial position was known. It is this particular type of case which is supposed to give the greatest difficulty in regard to both maternal and fetal outcome. This group will be discussed in detail later.

The causes of extension of the fetal head are manifold. It is obvious that fetal abnormality, prematurity, and minor variations in position of the spine and the occiput can cause extension of the fetal head. The last may possibly be the cause of the occasional occurrence of face presentation prior to the onset of labor as was first described in 1821 by Mme. LaChapelle. It is well known too that great parity with relaxation of the abdominal wall and changes in the uterine axis can serve as a causative factor. Pelvic disproportion of even minor degree may cause extension of the fetal head. The rare occurrence of tumor in the birth canal may be responsible and very occasionally placenta previa may play a causative role. Of particular interest in this series is the effect of parity and of contracted pelvis.

TABLE III. BROW PRESENTATION, POSITION ACCORDING TO RACE

	WHITE		NEGRO		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Right brow anterior	4	15.3	0	0.0	4	10.0
Left brow anterior	3	11.5	1	7.4	4	10.0
Right brow transverse	7	26.9	5	35.7	12	30.0
Left brow transverse	5	19.2	4	28.6	9	22.5
Right brow posterior	5	19.2	4	28.6	9	22.5
Left brow posterior	2	07.7	0	0.0	2	05.0
Total anterior	7	26.9	1	7.1	8	20.0
Total transverse	12	46.2	9	64.3	21	52.5
Total posterior	7	26.9	4	28.6	11	27.5
Total	26		14		40	

Tables IV and V show the distribution of the patients in both face and brow presentation by age and parity. A glance at these tables would seem to indicate that distribution according to parity is normal. However, when one compares the percentage of cases in each parity group with the clinic average as shown in Fig. 1, it becomes apparent that whereas the clinic showed

TABLE IV. FACE PRESENTATION, PATIENTS DISTRIBUTED ACCORDING TO AGE AND PARITY

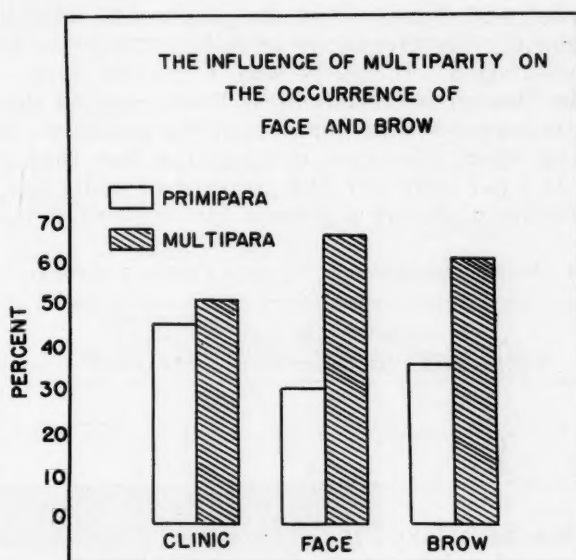| AGE (YEARS)	TOTAL	PARITY											
		0	I	II	III	IV	V	VI	VII	VIII	IX	X	UNKNOWN
14	1	1	–										
14-19	23	20	2	1	–	–	–	–	–	–	–	–	–
20-24	45	13	15	4	6	3	–	2	–	1	–	1	–
25-29	25	5	5	1	4	5	2	–	2	–	–	1	–
30-34	23	2	6	2	1	5	4	1	–	1	–	1	–
35-39	8	–	1	–	1	–	–	2	1	–	1	2	–
40-44	6	1	1	1	–	–	–	–	–	2	1	–	–
45+	–	–	–	–	–	–	–	–	–	–	–	–	–
Unknown	1	–	–	–	–	–	–	–	–	–	–	–	1
Total	132	42	30	9	12	13	6	5	3	4	2	5	1

Fig. 1.

47.1 per cent in primiparas and 52.9 per cent in multiparas, face presentation occurred in primiparas 31.8 and in multiparas 68.2 per cent, while the comparable figures for brow presentation were 37.2 per cent in primiparas and in multiparas, 62.8 per cent. It, therefore, appears that multiparity plays some role in the etiology of the extended head. Furthermore, if these figures are examined more closely, face and brow presentation show a greater number of patients in the high parity group, that is, above para iv, than is shown by the clinic population.

TABLE V. BROW PRESENTATION, PATIENTS DISTRIBUTED ACCORDING TO AGE AND PARITY

AGE (YEARS)	TOTAL	PARITY											
		0	I	II	III	IV	V	VI	VII	VIII	IX	X	UNKNOWN
14	–	–	–	–	–	–	–	–	–	–	–	–	–
14-19	6	4	2	–	–	–	–	–	–	–	–	–	–
20-24	7	6	–	1	–	–	–	–	–	–	–	–	–
25-29	11	4	1	1	4	–	–	1	–	–	–	–	–
30-34	4	1	1	1	–	–	–	1	–	–	–	–	–
35-39	12	1	–	–	1	2	1	1	–	1	1	3	1
40-44	2	–	–	–	2	–	–	–	–	–	–	–	–
45+	1	–	–	–	–	–	–	–	–	–	–	1	–
Total	43	16	4	3	7	2	1	3	0	1	1	4	1

TABLE VI. FACE PRESENTATION, TYPE OF PELVIS ACCORDING TO RACE

	NORMAL	INLET CONTRACTION	OUTLET CONTRACTION	INLET AND OUTLET CONTRACTION	TOTAL CONTRACTED	PER CENT
White	40	10	0	4	14	25.9
Negro	33	29	3	7	39	54.2
Total	73	39	3	11	53	43.1
Per cent	46.9	31.7	2.4	8.9	43.1	

The distribution of pelvic contraction in this series is shown in Tables VI and VII. The high incidence of contracted pelvis is striking in both races, but is particularly noticeable in the Negro. It would appear from analysis of the data that the important feature is contraction of the inlet of the pelvis rather than the outlet, and, hence, all of the graphs deal with inlet contraction. Fig. 2 shows graphically the frequency of inlet contraction by race, for both face and brow presentation. It can be seen from this figure that contracted pelvis is present in face presentation in 39.7 per cent of the cases, while in brow presentation it occurs in 53.8 per cent of the patients. These figures are particularly striking when one bears in mind the fact that pelvic inlet contraction occurs in 11.5 per cent and 32.4 per cent of white and Negro patients in this clinic, respectively, giving a general clinic average of 22.3 per cent.

TABLE VII. BROW PRESENTATION, TYPE OF PELVIS ACCORDING TO RACE

	NORMAL	INLET CONTRACTION	OUTLET CONTRACTION	INLET AND OUTLET CONTRACTION	TOTAL CONTRACTED	PER CENT
White	14	4	2	4	10	41.7
Negro	2	9	0	3	12	85.7
Total	16	13	2	7	22	57.9
Per cent	22.1	34.2	5.3	18.4	57.9	

Some authorities have taken the occurrence of face in the primipara as prima facie evidence of pelvic contraction and have advocated the performance of cesarean section forthwith. In this series face presentation occurred in primiparas 46 times, there being 30 Negro patients and 16 white. Of these, the pelvis was measured in 44, and the incidence of contraction was found to be 45.6 per cent. This is only very slightly higher than the average for the series and when one considers the high incidence of Negroes in this primiparous group, the two series present a very similar incidence of pelvic contraction.

TABLE VIII. FACE AND BROW PRESENTATION, COMPLICATIONS OF LABOR

	FACE	BROW
Uterine inertia	21	23
Prolapsed cord	6	3
Intrapartum fever	7	8
Placenta previa	1	0
Premature separation	0	1
Rupture uterus	0	2
Total complications	35	37
Total deliveries	141	45

Inasmuch as pelvic contraction was diagnosed by simple manual mensuration of the diagonal conjugate, and the pelvis was considered to be contracted if this measurement was 11.5 cm. or less, some question might be raised

as to the accuracy of the data presented above. Supporting evidence as to their validity is given by the fact that of 18 cases of face presentation receiving x-ray pelvimetry, five showed inlet contraction, while in eight cases of brow presentation subjected to the same type of measurement, four showed inlet contraction.

TABLE IX. FACE AND BROW PRESENTATION, MATERNAL INJURIES

	FACE	BROW
Third-degree laceration	0	1
Fourth-degree laceration	3	0
Vaginal laceration	9	6*
Cervical laceration	0	4
None	129	37
Total deliveries	141	45

*Six mothers had both cervical and vaginal lacerations.

TABLE X. FACE AND BROW PRESENTATION, POSTPARTUM HEMORRHAGE

	FACE	BROW
Deliveries	137*	41*
Hemorrhage	12	15
Per cent	8.8	36.6

*Four cases, amount of bleeding unknown.

FACE & BROW PRESENTATION
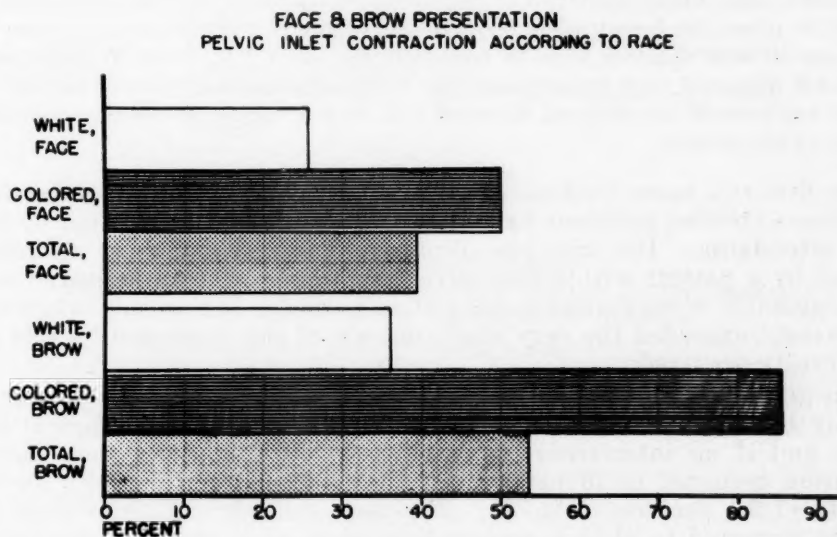PELVIC INLET CONTRACTION ACCORDING TO RACE

Fig. 2.

It has been stated that the presence of face or brow presentation predisposes to complications occurring during or immediately after labor. This would seem to be borne out by Table VIII which indicates a high incidence of uterine inertia, prolapse of the cord, intrapartum fever, and, in brow presentation, rupture of the uterus. However, the expected high incidence of trauma to the birth canal did not materialize. There was no increase in third- or fourth-degree lacerations of the perineum. Vaginal laceration was not particularly more frequent nor was cervical laceration (Table IX). Postpartum hemorrhage was not particularly more frequent in face than in the clinic popu-

lation at large. It did show some increase in the brow presentation but this was probably due to the high incidence of cesarean section in this group (Table X).

There were three maternal deaths in the series, all occurring in brow presentation. These are particularly instructive and will be presented briefly.

The first was a patient delivered in 1899. She was a white, 36-year-old multipara with a diagonal conjugate of 10½ cm. She was admitted after several attempts at delivery at home, and was, at that time, afebrile with no pains. The cervix was fully dilated and the child dead. Craniotomy was performed and a 3,120 gram fetus delivered. The patient developed a severe puerperal infection, a vesicovaginal fistula, and died on the twenty-sixth postpartum day of pulmonary embolus.

The second death occurred in 1935. This was a 41-year-old Negro para 3-0-0-3-0 with an unknown pelvis. She had been in labor at home for thirty-six hours, and had been fully dilated for fourteen hours. On admission, her temperature was 99.6° F. and pulse 120. A large fetus presented by brow. The cervix was fully dilated. Because the fetus was alive, immediate cesarean section and hysterectomy were performed. At delivery the uterus was filled with pus. Following delivery and during repair of the abdominal wall the patient died suddenly on the operating table. The child weighed 4,120 grams and did not survive. This death was taken to be an anesthetic accident.

The third maternal death occurred in a patient who was delivered in 1939. She was a 32-year-old para 6-0-0-0-5 who had a flat pelvis with a diagonal conjugate measured at 10.5 cm. Previous deliveries had been accomplished without difficulty but no child had weighed in excess of 3,200 grams. She had been in labor three hours on admission with the cervix 3 cm. dilated. No clinical disproportion was noted but the blood pressure was 200/115. She continued in labor, the hypertension being treated vigorously. Spontaneous rupture of the uterus occurred after fourteen hours of labor with the cervix 6 cm. dilated. Brow presentation was not diagnosed until hysterectomy had been performed and the child delivered. The operation was followed by puerperal infection with evisceration on the tenth postpartum day, and death on the eleventh.

The first two cases indicate the type of difficulty met by the obstetrician when these extended positions have been neglected and manipulated by incompetent attendants. The last case represents the type of false security engendered by a patient with a flat pelvis who has previously delivered several babies vaginally, even though smaller than normal. It was only when the infant's weight exceeded the very slight margin of size possessed by this pelvis that difficulty occurred.

It is generally known that the majority of face presentations deliver spontaneously or by easy low forceps, if allowed to labor for a sufficient length of time and if no interference is instituted. In this series such fortunate termination occurred in 75 per cent of the term pregnancies with an infant mortality of 9.1 per cent (Fig. 3). The more difficult deliveries from below would be expected to yield a greater loss; thus, mid- and high forceps were performed ten times with an infant mortality rate of 14.3 per cent. The combined incidence of difficult deliveries from below was 18.2 per cent with a fetal mortality of 16.7 per cent (Fig. 3). Version and extraction yielded good results in this series if the pelvis was normal and the membranes not too long ruptured. As a matter of fact not a single infant death occurred when version and extraction were performed with a normal pelvis. However, in the face of contracted pelvis the fetal results were deplorable, the infant loss being in the neighborhood of 50 per cent. It would appear that in the presence of this complication version and extraction have little place in modern obstetrics, as emphasized by Reddock, but in our opinion may occasionally be used to advantage. Cesarean section was performed for the most part on patients
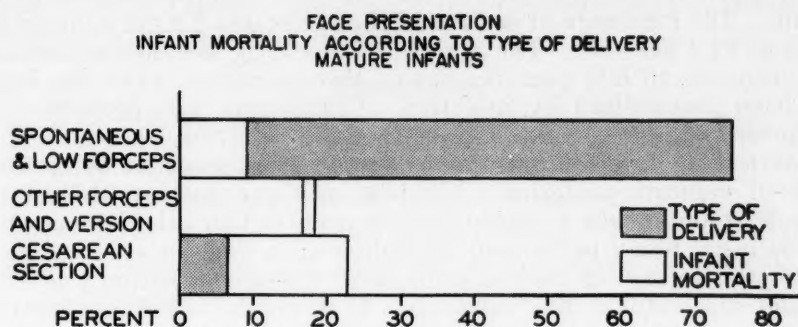
FACE PRESENTATION
INFANT MORTALITY ACCORDING TO TYPE OF DELIVERY
MATURE INFANTS

Fig. 3.

BROW PRESENTATION
INFANT MORTALITY ACCORDING TO TYPE OF DELIVERY
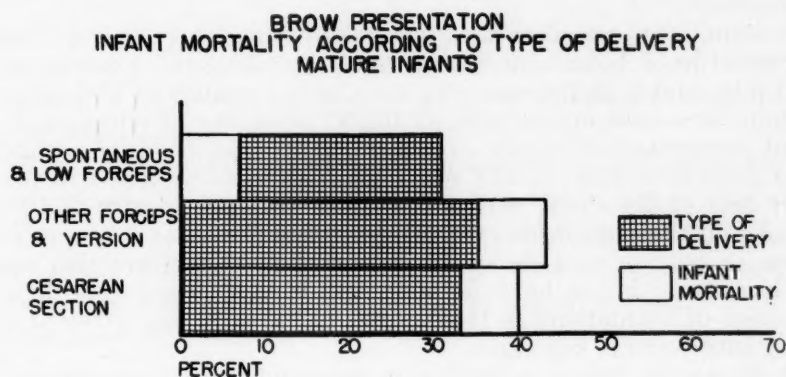MATURE INFANTS

Fig. 4.

FACE & BROW PRESENTATION
MORTALITY RATE FOR MATURE INFANTS IN NORMAL & CONTRACTED
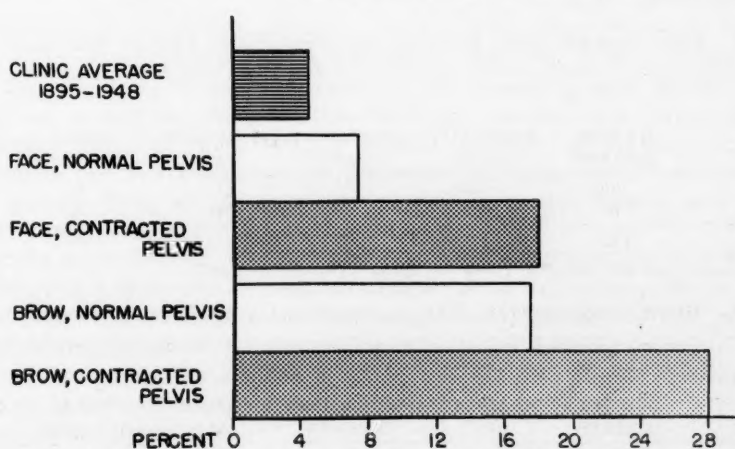PELVIS AS COMPARED TO THE CLINIC AVERAGE

Fig. 5.

with contracted pelvis, with uterine inertia, and with persistence of the posterior chin. The incidence of section in the series was 6.8 per cent with a fetal mortality of 22.2 per cent. The high fetal mortality in cesarean section seems to have been due to late performance of this operation, when the infant had already been jeopardized by infection. Craniotomy was performed in only two instances and both of these with the mentum anterior.

Of particular interest are the 39 instances of mothers with the initial diagnosis of mentum posterior. Nineteen of these patients delivered easily from below, spontaneous rotation having occurred in all of them and spontaneous delivery being performed in eighteen; in one, an easy outlet forceps was done. Conversion of the posterior face to occiput position was attempted in nine and successful in five instances. It is worth noting here that conversion was attempted also in six instances of anterior face presentation, being successful but two times. In the four cases of mentum posterior where conversion was unsuccessful, spontaneous rotation and delivery occurred in 50 per cent of these individuals. These findings are in accordance with the findings of Johansson.[5]

In 45 term brow presentations spontaneous delivery or low forceps delivery occurred in 31.1 per cent with a fetal mortality of 7.1 per cent. There were eight mid- and high forceps with an infant mortality of 37.5 per cent and eight versions and extractions with an infant mortality of 50 per cent, giving a combined percentage incidence of difficult deliveries from below of 35.6 per cent and a fetal mortality of 43.8 per cent. Cesarean section was performed in 33⅓ per cent of the cases, with a very high infant mortality of 40 per cent (Fig. 4). Again the high infant mortality in those cases of brow presentation would seem to be due to a delay in the decision to perform this operation, resulting in infants being born in poor conidtion. There were in addition three instances of craniotomy in this series. Conversion was attempted fifteen times, being successful in but eight.

Fig. 5 shows the infant mortality in face and brow presentation as it is related to pelvic contraction. In face presentation the total infant mortality rate was 7.3 per cent and 18 per cent, respectively, in normal contracted pelves; while in brow presentation it was 17.4 per cent in normal pelves and 28 per cent in contracted pelves. This compares with the clinic infant mortality in term babies for the entire period under consideration of 4.4 per cent. Striking indeed is the effect of contracted pelvis on fetal outcome in these extended positions.

TABLE XI. FACE PRESENTATION, MATURE AND PREMATURE* INFANT MORTALITY RATES

	MATURE INFANTS	MORTALITY RATE	PREMATURE INFANTS	MORTALITY RATE	TOTAL INFANTS	TOTAL INFANT MORTALITY RATE
White	56	8.9	5	20	61	9.8
Negro	76	13.2	4	50	80	15.0
Total	132	11.4	9	33.3	141	12.8

*A premature infant weighs 1,000 to 2,499 grams, inclusive.

TABLE XII. BROW PRESENTATION, MATURE AND PREMATURE INFANT MORTALITY RATES

	MATURE INFANTS	MORTALITY RATE	PREMATURE INFANTS	MORTALITY RATE	TOTAL INFANTS	TOTAL INFANT MORTALITY RATE
White	28	21.4	0	0	28	21.8
Negro	16	31.3	0	0	16	31.3
Total	44	25.0	0	0	44	25.0

Tables XI and XII show the high infant mortality rate in the series both for term and premature infants by race.

Conclusions

1. The approach to extended position of the fetal head should in the main be conservative as the great majority of cases will result in spontaneous or easy forceps delivery with a relatively low infant mortality.

2. All of these patients should be meticulously studied from the standpoint of pelvic contraction and x-ray pelvimetry should be performed on all of them when feasible.

3. If pelvic contraction exists, cesarean section should be performed in view of the extremely high fetal mortality when these positions are associated with contracted pelvis.

4. Version may still have some small place in the treatment of face and brow presentation, if the membranes have not been too long ruptured and the pelvis is normal. It is contraindicated in instances of contracted pelvis.

5. Attempts at conversion may be of some worth, although in this series only 50 per cent of the attempts were successful.

6. The concern exhibited by some authorities in regard to the fetal and maternal outcome in mentum posterior is not borne out in this series. Although 30 per cent of the face cases fell under this group spontaneous delivery occurred in half of them. Even in the others, where more difficult types of delivery were resorted to, the infant mortality was not unduly high and there were no maternal difficulties.

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4. Fink, K.: Monatschr. f. Geburtsh. u. Gynäk. 70: 29, 1925.
5. Johansson, H.: Monatschr. f. Geburtsh. u. Gynäk. 120: 122, 1945.

Discussion

DR. FRANK MOSKOWITZ.—I would like to ask Dr. Hellman whether or not we could evaluate the progress of labor somewhat differently. After all, in a face presentation, labor aggravates the condition. It is long drawn-out and exhausting, and usually when we wish to intercede we have a compromised mother or baby. If we could prevent descent of the head and hasten dilatation, would we not improve matters? If we should insert a bag to hasten dilatation, we would have enough dilatation and early, so that we could convert or even do a version. This, of course, applies to those cases that frankly have no contracted pelvis and in which we are not contemplating section.

When the head descends in labor with a vertex presentation, it is a sign of normal progress, but in a face or brow presentation, labor is the aggravating factor. As the head descends in these cases the deflexion becomes exaggerated. During this time, which is usually long and drawn out, the mother becomes exhausted and the baby compromised.

Attempts to change the attitude at this stage are difficult and fraught with danger.

If we could prevent descent of the head and hasten dilatation at the same time, do you not think our results would be better?

A Voorhees bag inserted early, when labor is established, would keep the head from descending, extending, and impacting, and would also hasten dilatation to a degree in which conversion or even version would be easy.

The time element is important since prolonged difficult labor leads to the elongation and thinning out of the noncontractile zone, with the gradual ''capping'' of the uterus due to the shortening of the contracting muscle fibers. It is in these cases that we encounter our difficulties.

I feel that earlier active interference would improve our results in these cases of deflexion attitude. This of course applies to those cases in which there is definitely no contracted pelvis and in which section is not contemplated.

DR. FRANK P. LIGHT.—I was struck by the difference between this experience with this problem as compared with ours at the Long Island College Hospital. Feeling perhaps that this was due to the marked difference in the clinic population—that is, the low incidence of Negro patients—I made a survey of our material at Kings County Hospital on the Long Island College of Medicine Division for the last fourteen years (1935 through 1948). There, 44 per cent of our patients were Negro.

In that time there were 23,832 deliveries. Among these were 36 face and 10 brow presentations, excluding abnormal fetuses and those weighing less than 1,000 grams.

There were 27 mature infants in the face group, with an infant mortality of 3.7 per cent. Nine were premature, with a 33.3 per cent mortality.

The total fetal mortality was 11.1 per cent which approximates Dr. Hellman's figure.

There were only 10 brow presentations, 7 of which were full term, with a fetal loss of 42.8 per cent. Three were prematures with no deaths. So our total fetal mortality in this group was 30 per cent.

Adding all extended presentations, face and brow, the incidence among the white is 1 in 513 and among the Negro 1 in 524. Face presentation alone occurred 1 time in 606 among the whites and 1 in 749 among the Negroes. The incidence for brow was 1 to 3,336 among the white and 1 to 1,747 among the Negro. Hence, if there is any racial predisposition to brow presentation, from our material, we should have to conclude that the Negro patients have that predisposition, just the opposite of what Dr. Hellman found in his material.

The most striking difference between our material and that just presented is in the incidence of contracted pelvis. Thirty-four patients delivered full-term infants (27 face and 7 brow). There was only one abnormal pelvis (flat rachitic) in this group, an incidence of 2.9 per cent. Hence, it may be stated that, in our material, contracted pelvis played no part in the etiology of face or brow presentation.

No patient in the entire group was delivered by cesarean section.

Our fetal mortality among all full-term infants during the last twelve of the fourteen-year period cited was 2.1 per cent.

In this small group of cases with face presentation, 15 have had 29 previous or subsequent deliveries, all of them occipital with the exception of one, which was a breech. No repeat face presentations occurred. Of the smaller group with brow presentation, 4 have had previous or subsequent deliveries, all of which were occipital.

It is our feeling that face presentation is rarely primary, but occurs as a result of labor, in the presence of deviation of the uterus from its normal axis. To us brow is simply a transition phase.

Treatment of this complication at the Long Island College Hospital has been standardized for many years. To us, the most important thing in the treatment of extended head presentations (brow or face) is the early recognition of the condition, by careful abdominal palpation. When extension is suspected it is checked by vaginal examination or x-ray or both.

When the diagnosis is made, we first try, if the membranes are intact, the abdominal maneuver of Schatz which has rarely been successful in our hands. However, we emphasize it as a teaching point, since an abdominal maneuver, external version, is so successful in other abnormal presentations, breech and transverse.

We do not interfere operatively as long as the membranes are intact, except in contracted pelvis, which is very rare in our material.

When the membranes rupture, an anterior face is allowed to proceed to spontaneous delivery, as most of them will do.

When the membranes rupture, a posterior face must be corrected, usually by flexion, rotation, or occasionally by version. It cannot be left as such.

With enough dilatation to admit two fingers, we use the Ziegenspeck maneuver. When this fails, which is rare, we use Braxton Hicks version.

When there is enough dilatation at the time the membranes rupture to admit four fingers, 6 to 8 cm., we have at our command the Ziegenspeck or Thorn maneuver, or anterior rotation. Failing any of these, we resort to Braxton Hicks version.

In the presence of complete dilatation, 10 cm., we use the Ziegenspeck or Thorn maneuver, or anterior rotation. If none of these can be accomplished, internal version and breech extraction may be resorted to, but are rarely necessary.

If this routine is followed, cesarean section is rarely, if ever, indicated in the absence of a contracted pelvis.

The next discusser will present the results with this routine which has been followed for so many years at the Long Island College Hospital.

DR. GLASS.—A review of our statistics at the Long Island College Hospital from 1920 through 1948 revealed 117 patients admitted to the obstetrical service with face presentations, exclusive of anencephalic monsters. One hundred of these occurred in multiparous women, and only seventeen in primiparas, thus emphasizing the fact that this abnormal presentation occurs much more frequently in multiparous women.

Sixty-five, or 55 per cent, were anterior face presentations: in 15, or 12 per cent, the chin was lying transversely and the remaining 37, or 30 per cent, were posterior presentations.

Among the 117 cases there were only eight with contracted pelves; seven were delivered by cesarean section, and in the remaining one a craniotomy was done for an impacted dead baby.

One hundred nine patients delivered from below; 69 rotated spontaneously; in 37 either the Ziegenspeck or Thorn procedure was successfully done to convert the extended face to a flexed head, depending upon the dilatation of the cervix at the time the membranes were ruptured. In three conversion failed and so version and extraction were done.

The infant mortality for the series was about 7, or 6 per cent. It was very interesting to note that the babies of two of the three patients subjected to version and extraction died. From our experience, which is indeed small, we are inclined to agree with Reddock that version and extraction is not a safe procedure in the treatment of face presentation, especially if the membranes have been ruptured for a long period of time.

We are of the opinion that face presentations offer no serious problem provided they are recognized early. Moreover, if the pelvis is adequate and the infant is of average size, face cases do well, whether anterior or posterior.

The former rotate spontaneously while the latter should always be treated by conversion as soon as the membranes rupture.

Dr. Hellman has pointed out that 5 per cent of fetal anomalies exist in face presentations, particularly anencephaly. Therefore x-ray examination of the fetus should always be done before during a cesarean section for contracted pelvis, in an attempt to eliminate the existence of a visible anomaly.

DR. HELLMAN (Closing).—The figures cited by Dr. Light give an extremely low incidence of face and brow and I would say that with this exception their material resembles ours to a marked degree. I gather from the incidence of 3.7 per cent of contracted pelvis in Dr. Light's series that there is a real difference in the material from this standpoint. I would think that his low incidence of extended position stems from this factor.

Dr. Glass did not cite his incidence but again the occurrence of contracted pelvis is less than 5 per cent which is about what we found in our white patients.

I was extremely interested in the question of posterior chin, and cited figures showing excellent results with spontaneous rotation. It was not in these cases that fetal death occurred in our series. We lost babies in other cases and frequently during labor.

In regard to the point brought up by Dr. Moskowitz I would say that I do not agree with his therapeutic measures, but the point brought up regarding the length of labor was of extreme interest because it raises the question of what kills these infants. At autopsy, on babies dying after delivery from the transverse position, one finds a definite pathological entity associated with compression of the organs of the thorax. The question was raised in our fetal mortality conference a week ago as to whether this same mechanism did not play a role in face and brow. In this latter group, one finds, on x-ray, distortion of the chest with extreme extension of the head, and one wonders whether this abnormal position may not compress the heart and lungs and thus play a role in fetal mortality.

In our series there were numerous attempts to hasten delivery with the use of bags. This is no longer done for it yielded very poor fetal results. Furthermore, the bags do not always hasten labor; in fact, quite the contrary frequently occurs. Labor is often poor and infection of rather frequent occurrence. We have practically given up the use of bags except in certain rare conditions. I, however, feel that the question of whether babies who present by face and brow should be subjected to long labor is a good one. Therapeutically speaking, I have no answer as to how to shorten these labors.

OVULATION IN LACTATING WOMEN*†

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CLINICALLY, it is a well-known fact that without using any contraceptive measures some women will not become pregnant during their period of lactation while others will. The conclusion derived from this fact is that ovulation may not occur in the former but does in the latter. This paper presents data on ovulation during lactation gathered from a study of 121 normal lactating women who were followed by means of repeated endometrial biopsies taken during their period of lactation amenorrhea and who were biopsied when they had their first postpartum period.

Little work had been done in the study of endometrial biopsies during the period of lactation. Kurzrok, Lass, and Smelser[1] took premenstrual endometrial biopsies from 48 lactating women in whom regular menstruation had already been established. In a total of 194 biopsies they found that 45 per cent showed secretory changes. Griffith and McBride[2] obtained biopsy specimens from 21 normal lactating women at frequent intervals and found that only one woman ovulated prior to the resumption of menstruation. Topkins,[3] in a study of 28 normal lactating women during the period of lactation amenorrhea, found that 94 per cent of the specimens studied showed proliferative changes and 6 per cent showed secretory or progestational changes.

Material

For this study a group of patients were selected from the postpartum clinics of the Michael Reese Hospital and the Chicago Maternity Center. Each patient was nursing regularly. As the study progressed, two main groups developed. The first group consisted of women who were amenorrheic throughout their period of lactation. During this period of amenorrhea, endometrial biopsies were repeated at two- to four-week intervals and from two to six biopsies were taken on each patient. The second group of patients included those women who had their first postpartum period while still nursing regularly. A biopsy was taken either just before the onset of the flow or sufficiently long afterward to indicate the presence or absence of cyclic ovarian activity.

On the basis of these biopsies a diagnosis was made of the phase of the menstrual cycle represented. At this point I would like to bring up the question of terminology in describing the phases of endometrial growth. While it has become common practice to use the words proliferative and secretory when referring to preovulatory and postovulatory phases, respectively, in a communication with Dr. Bartelmez‡ he pointed out that these terms are not entirely in accord with the present evidence of cellular activity of the endometrial glands. He points out that for a period of time following menstruation there may be little or no evidence of actual proliferation. Moreover, to use the word secretory for the postovulatory phase is not entirely correct since secretion occurs even in the preovulatory phase. Accordingly he feels that the terms "estrogenic phase"

and "luteal phase" are preferable. With this the author is in full accord and
henceforth these terms will be used in this paper.

The presence of a luteal endometrium implied that ovulation had taken
place. The demonstration of an estrogenic endometrium repeatedly in the phase
of lactation amenorrhea implied the absence of ovulation while the presence of
an estrogenic endometrium from one to ten days before the onset of bleeding
implied an anovulatory cycle. When estrogenic endometrium was obtained
from twenty to forty days after the first period it was presumptive evidence
that cyclic activity of the ovary was not yet established.

The technique for obtaining the endometrial biopsy is simple and can be
carried out with practically no discomfort to the patient. With the patient in
the lithotomy position, the cervix is wiped clean with sterile cotton pledgets
and the external os and canal painted with a two per cent tincture of iodine
solution. After the size and position of the uterus are determined by a bimanual
examination, the biopsy curette is introduced until the fundus is felt, then four
strips are taken. It was unnecessary to use suction although at times a Luer
syringe was used to blow the tightly packed tissue out of the curette into a jar
of 4 per cent formalin. Then it was fixed, cut, stained. mounted, and reported
on by Dr. Otto Saphir, Director of Pathology at Michael Reese Hospital.

Occasionally spotting followed a biopsy but it was always mild and rarely
lasted more than a few hours. In over 500 biopsies no accident was encountered.

Results

Part I.—Of the 200 biopsies taken on 85 lactating amenorrheic women, 197,
or 98.5 per cent, were estrogenic and 3, or 1.5 per cent, were luteal endometria.
In each case the luteal endometrium was associated with the onset of the first
menstrual period. In Case 16. biopsies taken at the tenth and twelfth post-
partum weeks returned estrogenic endometrium, but the third taken at the fif-
teenth week was luteal endometrium. This was followed in seven days by a
menstrual period. In Case 70, three previous biopsies taken at forty-three,
forty-five, and forty-eight weeks were estrogenic endometrium, but the fourth
biopsy taken at the fiftieth week was early luteal endometrium. This was fol-
lowed in twenty-four days by a menstrual period. In Case 75, one previous
biopsy taken at the fourteenth week was estrogenic in nature but the second
biopsy taken at sixteen weeks was late luteal, and this was followed one day later
by a menstrual period.

Of the 197 specimens of estrogenic endometrium some were poorly developed.
In some cases, where small atrophic uteri were found after long periods of lac-
tation from six to eighteen months, the endometrium shared in the general
atrophy of the uterus and many strokes were made with the curette before
sufficient tissue could be obtained for examination. In some cases it was not
possible to get enough tissue for diagnosis.

Most of the 197 specimens of estrogenic endometrium presented the char-
acteristics of the mid-follicular phase of development as might be found in the
first week of the menstrual cycle or, as described by Markee,[4] the primary growth
phase. The endometrium usually presented narrow straight glands, lined with
low columnar or cuboidal epithelium. The stroma was compact and avascular.
Usually there was no serous secretion although in twenty cases. or 10 per cent,
there was evidence of late estrogenic phase in which the glands were larger,
wider, and more tortuous, the stroma less compact. The nuclei remained basal
in most cases although in some, migration toward the lumen of the gland was
noted. The characteristic feature of 90 per cent of the specimens obtained in
this group of lactating amenorrheic women was the lack of progression or growth.
Instead, repeated biopsies taken from the same patient at weekly and monthly
intervals revealed the static nature of the endometrium with a persistence of
the estrogenic phase.

Part II.—Thirty-six of the 121 lactating women studied had their first post-partum period while nursing regularly. Sixteen of these patients were biopsied one to ten days before the onset of bleeding and twenty were biopsied twenty to forty days following the onset of bleeding. In only five, or 14 per cent, was there evidence of ovulation. Three of the sixteen premenstrual biopsies were luteal and two of the twenty postmenstrual biopsies were luteal.

Discussion

Inasmuch as the endometrium reflects the secretory activity of the ovary, the finding of persistent estrogenic phase in 98.5 per cent of the 200 biopsies taken during lactation amenorrhea indicates an almost complete suppression of follicle maturation and ovulation by some factor or factors during lactation. If one glances at slides taken at regular intervals in a normally menstruating woman the continuous progressive changes in the primary and secondary growth phases, as indicated by Markee, are striking. Conversely, the stationary or static nature of the endometrium in lactation amenorrhea, as has already been noted by Topkins and others, is also very impressive and would seem to imply neither maturation nor regression of the ovarian follicle, but rather a state of "follicle stasis."

The occurrence of menstruation following all three cases where luteal endo-metrium had been obtained during lactation amenorrhea bears out the conten-tion of Rock and Bartlett,[5] who in a study of 300 luteal biopsy specimens found only two cases which were not followed within sixteen days by menstruation and in one of these menstruation occurred twenty days after the biopsy. In these three patients in this study who ovulated during the phase of lactation amenorrhea is found the answer to the oft-asked question, can women become pregnant during lactation in the absence of menstruation? The answer is, of course, yes, in about 3.5 per cent of the cases where the first ovulation is followed immediately by conception. The ensuing pregnancy prevents the onset of men-struation which would otherwise invariably follow ovulation.

In studying forty-eight lactating women in whom regular menstruation had been re-established, Kurzrok and others found that 45 per cent of the cycles were ovulatory in character. The problem attacked in Part II of this study is, "What is the nature of the first postpartum period during lactation?" Since resump-tion of a normal endocrine pattern in the female usually requires more than one cycle for complete restitution it was anticipated that these studies would not reveal ovulatory cycles in a large number of cases. Of the small series of thirty-six women who had their first postpartum period while nursing regularly, premenstrual biopsies were obtained in sixteen from one to ten days before the onset of menstruation. Only three of these were luteal. The other twenty lac-tating women were seen after they had had their first postpartum period. Since Kurzrok had shown that once an ovulatory type of lactation menstruation appeared it usually persisted, it was reasoned that if ovulation had preceded the first period, there would be definite luteal endometrium present within twenty days postmenstrually if normal ovulatory activity were present. Accordingly, postmenstrual biopsies were taken from twenty days on after the first period. Of these twenty postmenstrual biopsies, only two showed evidence of luteal activity. Therefore, in only five, or 14 per cent, of thirty-six lactating women in whom menstruation had been resumed was there evidence of ovulation either preceding or immediately following the first postpartum period. Unfortunately, it was not possible to have these women return for a further follow-up of their menstrual history. Of the remaining thirty-one women, five were known to have become pregnant in three months. This would bring the known evidence of ovulation to well above twenty-eight per cent within three months, indicating that the figure of forty-five per cent ovulatory cycles in regularly menstruating lactating women as stated by Kurzrok is soon attained.
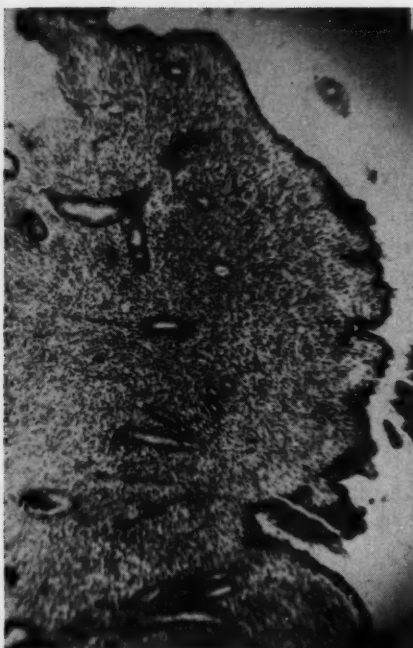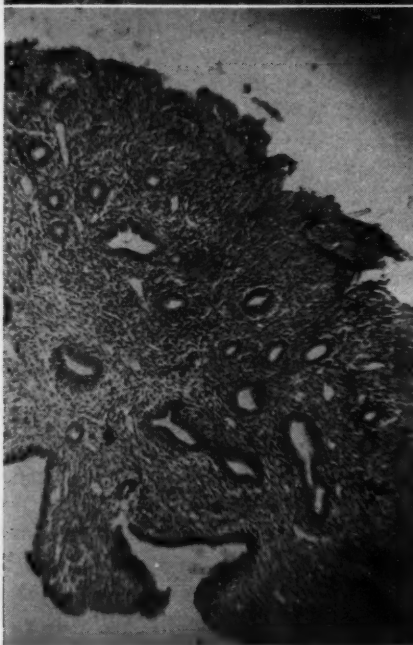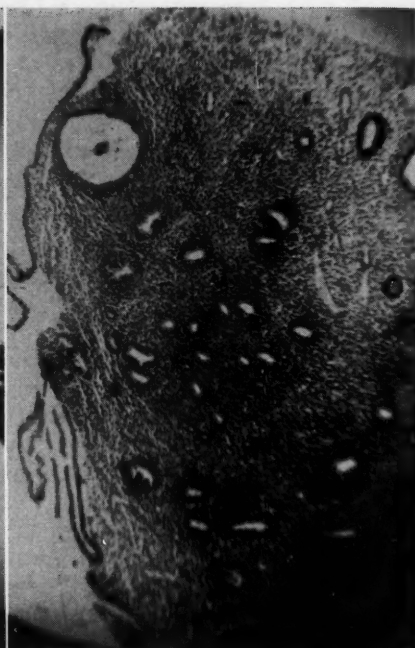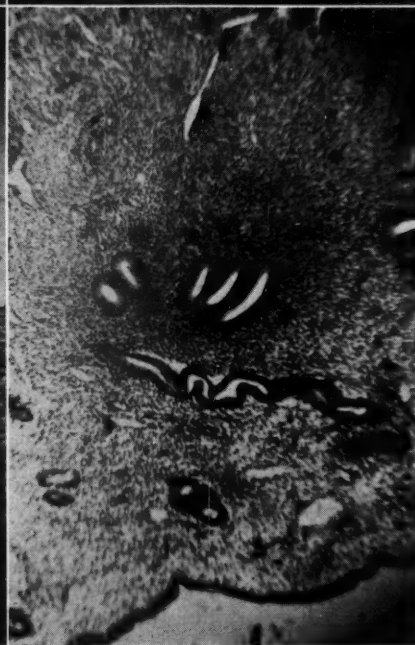
Fig. 1.	Fig. 2.

Fig. 3.	Fig. 4.

Fig. 1.—Mrs. A. B. Estrogenic. Six weeks post partum.
Fig. 2.—Mrs. A. B. Estrogenic. Eight weeks post partum.
Fig. 3.—Mrs. A. B. Estrogenic. Twelve weeks post partum.
Fig. 4.—Mrs. A. B. Estrogenic. Sixteen weeks post partum.

It is interesting at this time to conjecture as to the nature of the factors during lactation which inhibit ovarian activity and produce lactation amenorrhea. The anterior lobe of the hypophysis elaborates a hormone, prolactin or luteotrophin which is antigonadal in lower animals as demonstrated by Lahr, Bates, and Riddle.[6, 7, 8] In a very interesting work on the rat, Desclin[9] points out that structural changes of the pituitary occur during lactation. Animals were spayed at delivery and divided into a group which did not suckle and a group which suckled their young. Ten days later all were killed. Those which did not suckle showed very definite castration signs in the hypophysis. Injection of prolactin did not prevent castration cells from appearing. In those animals which suckled no castration cells made their appearance. This result indicates that lactation alters the secretory activity of the hypophysis.

In another interesting experiment,[9] infantile ovaries were implanted into the kidneys of spayed lactating and nonlactating rats. In lactating animals the implants were small and contained young follicles without corpora lutea. In the rats the young of which had been removed from breast, the implants had enlarged enormously and contained numerous corpora lutea.

The role of prolactin has of late been stressed. It has been shown by many authors[10, 11] that the injection of the lactogenic hormone inhibits the estrous cycles in the rat and mouse. In studying the antigonadal action of prolactin in birds, Lahr and Riddle[12] believed that prolactin is an antagonist of female sex hormone and saw in this property an explanation of the antiestral action of prolactin in the mammal.

The antigonadal properties of prolactin, produced in the pituitary under the influence of suckling, could explain the results in the ovarian graft experiment. However, if the peripheral action of prolactin were the only factor involved in lactation amenorrhea, then the production of castration cells in the pituitary of nonnursing rats spayed at delivery should be prevented by injection of prolactin. Desclin's experiments show conclusively that this is not the case. Therefore, there must be a direct influence of suckling on the secretory activity of the hypophysis.

Summary

1. Two hundred endometrial biopsies were taken from eighty-five normal lactating women who were amenorrheic.

2. Of the 200 endometrial biopsies, 197, or 98.5 per cent, were estrogenic and 3, or 1.5 per cent, were luteal in character.

3. In all three cases the luteal endometrium was followed by the onset of the first menstrual period.

4. Thirty-six lactating women were biopsied either just preceding or following the first postpartum period.

5. Evidence of ovulation was found either preceding or following the onset of the first period in five women, or 14 per cent.

6. The relationship between lactation and ovarian function is discussed.

Conclusions

1. In lactation amenorrhea the suppression of the ovarian cycle is almost complete.

2. When ovulation does occur, it invariably heralds the approach of a menstrual period unless a pregnancy intervenes.

3. During lactation menstruation the suppression of the ovarian cycle is gradually lifted so that 14 per cent ovulation occurred in the first postpartum period in this investigation and over 28 per cent ovulation occurred after three or more periods.

4. Suckling has a direct influence on the secretory activity of the hypophysis leading to the production of prolactin plus some unknown factor which inhibits the ovarian cycle.

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Discussion

DR. RACHMIEL LEVINE.—Most of what I have to say will possibly be speculative, since the endocrinology of lactation is at present one of the most confusing subjects in the field.

Experiments have proved definitely that androgens are necessary in the development of the breast; also that estrogens are necessary. It has been shown that estrogens cannot develop the breast in the absence of the hypophysis, and there is just as conclusive evidence that estrogens can do so in the absence of the hypophysis. You will find experiments in which it is shown that the anterior pituitary through mammogen I and mammogen II actually produces proliferation of the breast, and that it is not due to the androgens or estrogens. You will also find experiments in which mammogen I and II are ascribed to the imagination. You will then encounter a substance known by the name of prolactin or lactogenic hormone, which is not needed for the growth and development of the breast but is necessary for the initiation and maintenance of lactation. Everybody agrees that it is necessary for the maintenance of lactation and that the pituitary gland has an increased amount of it during pregnancy and during lactation. A few years ago it was shown that in some species this same hormone maintained the function of the corpus luteum and led to the secretion of progesterone from it. From that time on the lactogenic hormone has been known as leuteotrophic hormone.

Why should lactation suppress the sex cycle? It seems to me that Dr. Udesky's results are contradictory. It is true that he found that in over 90 per cent of his cases lactation was accompanied by amenorrhea, and evidence from his slides demonstrated that there was some estrogen secretion. I would surmise that the ovary was quiescent, that it had follicles and a nonfunctioning corpus luteum. However, in some cases the cycle breaks through despite the continuation of lactation, and he showed again that when it does break through it can become a fully normal cycle with ovulation and menstruation and secretory endometrium, despite the fact that lactation goes on. In other words, you can have lactation with suppression of the cycle and then the cycle will break through despite the fact that the conditions for lactation are present and lactation proceeds.

We have to conclude that something at the end of pregnancy—something perhaps in the pituitary—has been suppressed, that lactation will maintain that status for a certain time, or the cycle will break through and then the two phenomena can go on together for a while, both maintenance of lactation and normal cycles.

I wish that Dr. Udesky would follow this work up with some evidence other than histologic. In other words, does the human being operate like some animals that have functioning corpora during lactation? Do they metabolize progesterone? Will progesterone change the endometrium into a secretory one? What is the pregnandiol yield during lactation amenorrhea?

DR. RONALD R. GREENE.—This was a well-planned and a well-executed piece of research. Granted that it confirms something that had been clinically suspected for a long time, this is objective evidence, that evaluation occurs with great rarity in amenorrheic lactating women and that, even if the woman has bleeding, ovulation is still quite rare.

I dislike the word "estrogenic." To me, the estrogenic hormone is one that stimulates growth of the endometrium. Growth is an activity. It infers division of cells, and there are mitotic figures in the endometrium during the growth phase. Dr. Udesky describes the majority of these specimens of endometrium as being inactive, showing small minute glands with low epithelium but no mitotic figures. A previous worker who did similar work on the subject described essentially the same picture and may I very tentatively and with all due regard to Dr. Bartelmez, suggest the word "resting" for this endometrium. Obviously, with this same picture week after week with no growth and no progression, it is hard to conceive of its being under the influence of much estrogen.

Several of the biopsy specimens were extremely inactive as described. However, I was impressed in several of the specimens by a picture that resembles mild hyperplasia rather than the normal proliferative phase. In one specimen the surface epithelium had two areas with piling up of the epithelium. One was identical to a "syncytial-like metaplasia" as described by Novak. In this specimen were many mitotic figures. Many of the nuclei in the superficial portion of the stroma were round and thick as are normally seen in the early secretory phase. This lack of correspondence between the stroma and glands is found in some hyperplasias. Another specimen showed very frank hyperplasia. In several separate areas there was crowding together of the glands with no intervening stroma. Extremely active-appearing epithelium and stroma were present in all fields.

One other thing needs clarification: the luteotrophic effect of prolactin. It is the current custom in teaching and in the journals to speak of this as being *the* luteotrophic hormone, meaning luteotrophic in the human being. To my knowledge there is no evidence that prolactin has such an effect in the human being. It is known that in some experimental animals there is functionally active corpus luteum during lactation, as in the rat and mouse. In other animals, namely, the dog and the human being, there is no evidence to my knowledge that there is a functioning corpus luteum during lactation. In the rat and mouse where there are corpora lutea while prolactin is produced, the prolactin is probably luteotrophic. You can administer prolactin to normally cyclic animals and stop the cycles.

In the human being it is quite easy to demonstrate the luteotrophic effect of chorionic gonadotropin and this has been done by several groups of workers. Large amounts have been given to normal cyclic females during the last half of the cycle when they have a corpus luteum. The onset of menstruation is delayed, pregnandiol continues to be produced. To my knowledge there is no evidence that prolactin has any such effect in the human being and I have been informed that several individuals have tried to demonstrate this. I think that in our various journals and in our teaching we should not speak of prolactin as being the luteotrophic hormone.

DR. GEORGE W. BARTELMEZ.—Dr. Udesky has used the only practical method we have at the present time for diagnosing ovulation in the intact human being. The method has its disadvantages and it is laborious. Certainly, it has not been replaced by the basal temperature method. The only work so far as I know on that method which provides crucial evidence is the report on thirty young women on whom sterilization procedures were contemplated. Basal temperatures were taken for several cycles and all patients were brought to surgery at the anticipated time of ovulation. Fourteen out of the thirty showed no visible signs of large follicles or recent corpora lutea (Greulich, Morris, and Black: Conf. Probl. Human Fertil, pp. 37-66, 1943).

The evidence which Dr. Udesky has given us that there are the two kinds of endometrium in the amenorrhea of lactation is significant. One of these types I should like to call "inactive." It has a dense stroma in which the cells are closely packed. It does not appear to have begun to grow. You may recall that Markee, in his study of endometrial transplants, described a phase following menstruation during which there was

little or no growth. He found that it might last only a few hours or up to ten days. In the macaque monkey we were able to show that this delayed ovulation is by no means an infrequent occurrence, and we had some cases in which ovulation occurred between twenty-one and thirty-six days after the onset of the previous period (Rossman and Bartelmez: AM. J. OBST. & GYNEC. 52: 28, 1946). During such postmenstrual periods, there is no sign of ovarian activity. This is similar to the inactivity during lactation in women.

The other type of endometrium has a loose stroma and mitoses. In the macaque monkey, in the early growth phase, we have found up to 6 per cent of epithelial cells dividing.

The identification of the inactive phase is not difficult. I do not think that is true of the follicular phase or of the so-called secretory phase. You will pardon a momentary digression into terminology. Schroeder introduced the terms ''proliferative'' and ''secretory.'' There is, however, active secretion during his proliferative phase. The glands are not swollen, I believe, because myometrial activity keeps them empty. The secretion produced is of real importance. In the macaque it contains both mucins and glycogen. On the other hand mitosis continues into the luteal phase. In 1923, Corner described a case with a 6-day corpus luteum in which there was abundant epithelial mitosis. Neither mitosis nor secretion are therefore distinctive of these two phases. I would suggest the use of the terms introduced by Courrier in 1924, namely, ''follicular'' and ''luteal'' phases. There is some uncertainty in using the endometrial picture as evidence of ovulation. In 1926 Stieve obtained material from a panhysterectomy. The endometrium was diagnosed by Robert Meyer as typical of a three and one-half weeks' ''secretory'' stage. There was, however, no corpus luteum, only a large Graafian follicle. In the material which we obtained from Dr. Carey Culbertson, there was a case from a panhysterectomy obtained on the second day of a period which had appeared as expected. One region of the endometrium was definitely inactive and would be diagnosed without question as anovulatory menstruation. In the fundus, on the other hand, the endometrium was of the luteal type. There was no corpus luteum in either ovary, only a follicular cyst; the follicle had not ruptured but it contained some cells of the luteal type. A biopsy in such cases would be misleading.

The possible error then in considering the frequency of ovulation during lactation is on the side of diagnosing too many ovulations, particularly since Dr. Udesky has shown us that the cycles during lactation are atypical at first. They gradually approach the typical. This is Hartman's staircase phenomenon (1932).

It may be worth while to call attention to some conditions described in other mammals. In the macaque the amenorrhea of lactation is complete. The uterus and ovaries revert to essentially the juvenile state and there is no evidence of activity for the lactation period which averages seven months. Hartman never saw a reappearance of activity earlier than five months after delivery. The same picture has been described for the baboon with one striking difference: Hartman's lactating monkeys had a brilliant red sex skin such as is usually associated with high estrogen in the blood. The uterus shows no trace of estrogen response. In the baboon, which Gilman and Gilbert (1946) studied in detail both sex skin and ovaries are inactive during lactation. Obviously we do not know much about the relationship of endocrines and lactation.

Dr. Greene has referred to conditions in rodents. In the rat and mouse there is regularly an ovulation soon after parturition. In the wild it apparently never results in pregnancy but under laboratory conditions it does. Such eggs then may be fertilized. They cleave, pass down the tube, develop into blastocysts in the uterus and then they stop developing. In the mouse the period of inactivity may persist for fourteen days. When weaning begins the eggs resume development and two weeks later a normal delivery occurs. We are dealing here with the effect of the anterior lobe of the hypophysis on the developing eggs free within the cavity of the uterus. It is difficult to see how the eggs can be influenced except by way of the uterine secretions. The phenomenon of delayed implantation is not rare in mammals. There are some in which the period of delay is longer than the actual period of gestation. There are species which normally ovulate and

have postpartum periods of heat but never become pregnant. In other words, there are many factors concerned in the mechanism of lactation and they differ in different mammals, as Dr. Levine has said.

Finally, I wish to commend such an attack on fundamental problems by clinicians who have a background of objective experience which no one is likely to acquire in the laboratory.

DR. M. EDWARD DAVIS.—In 1942, Dr. Scheitema and I carried out a series of observations on women delivered at the Chicago Lying-in Hospital, the object of which was to determine the pattern of ovarian activity following parturition. Serial biopsies of the endometrium were made six weeks after delivery and at the onset of each bleeding period until a regular menstrual pattern was established. A total of fifty women were followed for an average of one year. Women who continued to nurse their infants beyond the first six weeks were excluded from this study. The endometrial biopsies were carefully prepared in the usual way as well as to determine the presence of glycogen.

Studies of the endometrium revealed that the first bleeding period was rarely ovulatory. The second bleeding period was ovulatory in character in about 50 per cent of our patients. However, in almost the entire group the third menstrual period was associated with typical progestational changes.

We concluded that the resumption of ovarian activity following parturition in women assumed the same character as at puberty and adolescence and at the menopause. The process, however, is much more prolonged at the two extremes of the reproductive period. The general stepladder-like pattern for the initiation of ovarian function in early life, and its cessation at the climacteric is witnessed in the resumption of ovarian activity following childbirth.

DR. JOHN BREWER.—Did the four biopsy strips taken from the uterus show the same histologic picture in all four biopsies?

Did the repeated biopsies at two-week intervals produce any demonstrable infection or inflammatory reaction in the endometrium?

What was the longest time after delivery that you found any hyaline or collagenous material within the endometrium?

DR. UDESKY (Closing).—In response to what Dr. Levine said about the occasional ovulation that breaks through during lactation one clue was apparent to me, that when ovulation occurred it usually was in the patient in whom lactation had been present for three or four months at least. It seemed to me that the intensity of the suckling and lactation process had a direct bearing upon the occurrence ovulation. Following that through, I began to study the effect of weaning on the endometrium and so far eleven women have been followed during the weaning process and are still amenorrheic. I did biopsies on these patients and I was astonished to find that of these eleven, four had a luteal type, two a late estrogenic, and four were of the type we showed here, so there was an increased incidence of ovulation as soon as the weaning process went into effect. That is why we all know women who become pregnant while they are lactating.

In response to Dr. Brewer's questions, there were different pictures in the histologic sections from the various parts of the uterus. They were not all the same and many presented different phases. One would appear to be a later phase and at other times earlier; I found that at one time it resembled a late proliferative estrogenic phase and two weeks later a lesser degree of the estrogenic phase. As to inflammatory reaction, I do not know how to answer that; I saw several instances of this reaction but I do not know whether they were due to the biopsy. The longest time I saw hyaline plaques within the endometrium was thirteen months after delivery.

THE USE OF ULTRAVIOLET LIGHT AND FLUORESCENT DYES IN THE DETECTION OF UTERINE CANCER BY VAGINAL SMEAR

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THE cytological study of vaginal smears as a screening method in the detection of uterine cancer is now an established laboratory procedure.[1] This is a preliminary report of a new diagnostic technique whereby vaginal smears are stained with fluorescent dyes (fluorochromes) and observed microscopically with ultraviolet light as a source of illumination. Acidic and basic fluorochromes act specifically to stain certain cellular structures as do the more common microscopical stains as hematoxylin and various aniline dyes. Whereas smears stained with the latter dyes are ordinarily examined in transmitted light of the visible spectrum, fluorescent stains remain practically colorless until irradiated with ultraviolet light. Cells stained with fluorochromes absorb the ultraviolet rays of short wave-length, and emit this energy in the form of fluorescent light in the visible spectrum. These cells fluoresce brightly and clearly with well-defined nuclear and cytoplasmic structure. The color and intensity of fluorescence depend on the characteristics of the particular stain and the relative acidophilia and basophilia of the individual cells.

Many investigators have published papers on the application of fluorescence microscopy to histological problems, of which only a few will be mentioned.[2-6] Fluorescent-stain microscopy has been applied to the diagnosis of tuberculosis,[7] and to the identification of malarial and other protozoan parasites.[8,9] Techniques for photographing fluorescent phenomena have been discussed.[10,11] Several books have been written on the subject of ultraviolet fluorescence and its applications.[12,13,14]

Method

The apparatus necessary for fluorescence microscopy is simple and inexpensive. A good source of illumination, which must be rich in the ultraviolet region 3,000 Angstrom units to 4,000 Angstrom units, is the General Electric H4 mercury vapor lamp. This fits into an admedian screw base socket that may be mounted in any type lamphousing. In our experience the AH4 was superior to the BH4 and CH4 mercury vapor lamps for microscopic work. It was observed that a more intense source of ultraviolet light was obtained for microscopy by removing the larger of the two glass lens systems of the lamphousing (Fig. 1) located immediately behind the iris. The baffle system depicted is not necessary, and was added to the lamphousing to prevent the escape of visible light as this same apparatus was used for a source of ultraviolet illumination in macroscopic fluorescent photography.

Photomicrographs of vaginal cells stained with fluorescent dyes and illuminated with ultraviolet light in Figs. 2, 3, 4, and 5 were made with the apparatus seen in Fig. 1. Black and white pictures were made using Panatomic-X film;

four to six minutes' exposure time; 4.5 lens opening set to a distance of infinity; achromatic objective 4 mm., 0.65 N. A. 43X; and 10X ocular. A 16-mm. dark-field stop and a doubled exposure time were found advantageous if glare due to the presence of a large amount of mucoid material was apparent. Daylight type Kodachrome color film has given excellent duplication of the fluorescent colors depicted in vaginal cytology when used in the Kodak 35 mm. camera with twelve to fourteen minutes' exposure time and a similar lens system as aforementioned for black and white photography. Since the nuclei of fluorescing cells are much brighter than the accompanying cytoplasm, much nuclear detail seen microscopically is lost in photographing due to relative over-exposure so that cytoplasmic detail may be recorded. Figs. 6 and 7 were made with a Mercury camera, lens removed, with an exposure time of eight minutes.
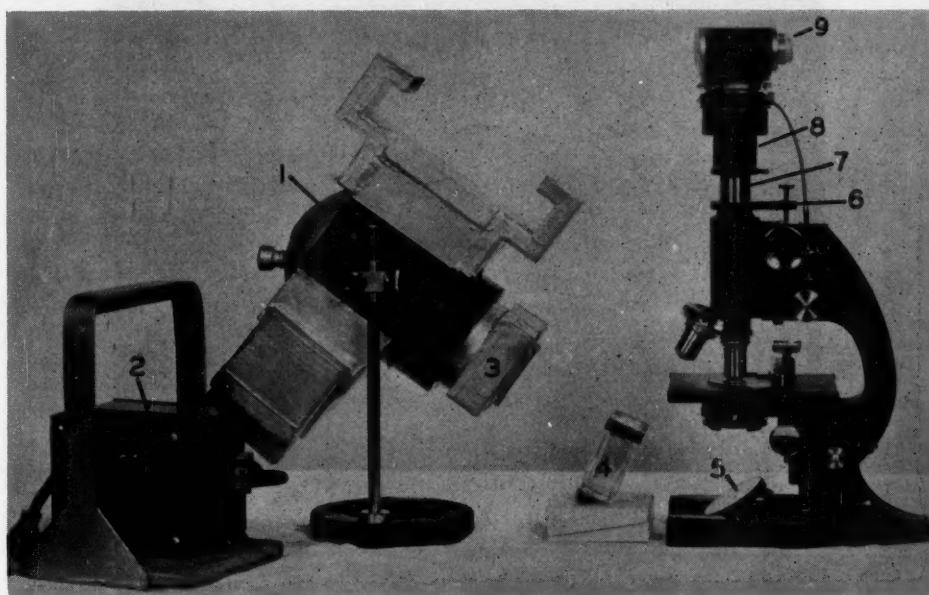

Fig. 1.—Shows the AH4 lamp in a Spencer Model 370 lamphousing (1) which operates from a special transformer (2). A UG-4 Schott filter (3), Fish-Schurman Corp, approximately 5 mm. in thickness is placed in front of the lamphousing lens system. This filter removes all visible light (except a little red-purple which does not interfere, but may be eliminated by a glass cell (4) filled with 5 per cent copper sulfate solution acidified with a few drops of concentrated sulfuric acid) and all ultraviolet rays shorter than 3,100 Angstrom units. The smooth surface of the glass microscopic mirror (5) can be used, but replacement by an aluminum-faced mirror offers some advantage since the latter has a higher reflectivity for ultraviolet light. A protective Eastman Kodak Wratten 2A filter (7) inserted into the ocular of the Bausch and Lomb microscope filters out any stray ultraviolet light while simultaneously allowing the visible fluorescent light to pass freely to the observer's eye. An Eastman Kodak 35 mm. camera (9) is maintained in position with an ocular adapter (8) and held in focus by an ocular clamp (6).

Twenty-five fluorescent dyes in various stain combinations and in different pH staining solutions were investigated in developing a suitable stain. The combination of neutral berberine sulfate (Mallinckrodt), acid fuchsin (National Aniline), and acridine yellow (Grübler) has thus far proved best for definition of nuclear structure and differentiation of acidophilic and basophilic cells. Berberine sulfate (an alkaloid) is a basic fluorochrome that imparts a brilliant yellow-white fluorescence to nuclei. Acid fuchsin (a triphenylmethane dye) is an acidic dye that yields a red-purple fluorescence to the cytoplasm of certain cells. Acridine yellow (an acridine derivative) in the presence of a pH 8 buffer acts as a nuclear and cytoplasmic stain in various types of cells, superimposing a greenish-grey tint to some nuclei and orange-red to brown color in the cytoplasm of certain cells.

Smears are made by placing a drop of cervical mucus, or preferably scrapings directly from a suspicious area, on an ordinary high-quality microscopic slide. A round applicator stick is used to roll the specimen back and forth over the slide with a to-and-fro twirling motion of the thumb and index finger. Slides with thin, even distribution of the sample give best results. Before drying, the slides are placed in a solution of equal parts 95 per cent alcohol and ether, and left for at least fifteen minutes before staining as follows:
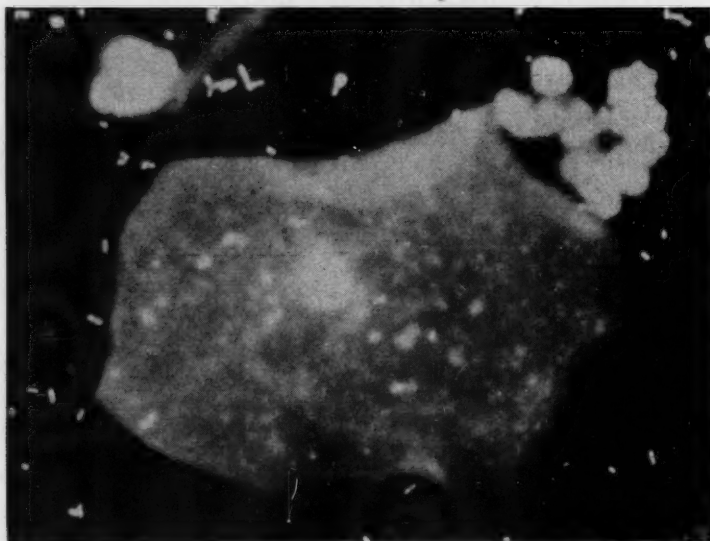

Fig. 2.—Normal, large, superficial squamous epithelial cell showing a small, pyknotic nucleus and curling of the cell's border. The nucleus fluoresced green-white and the cytoplasm green-brown. Note the polymorphonuclear leucocytes and bacteria of the vaginal flora in the background. (×2,000.)
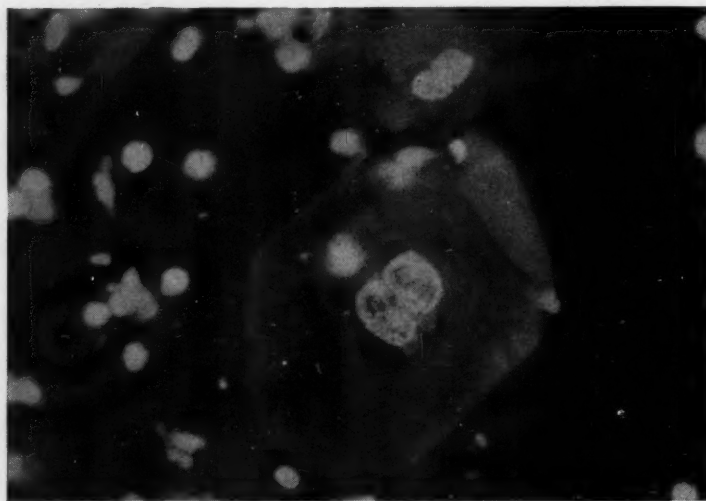
Fig. 3.—A superficial, epithelial giant tumor cell is located in approximately the center of the microphotograph. The bilobulated nucleus showing marked chromatin blocking fluoresced bright yellow-green and contained several reddish-orange nucleoli. There was an orange-colored area adjacent to the nucleus while the remainder of the cytoplasm appeared bright green. Note the smaller basal-type cells, the brightly fluorescent leucocytes, and the dark outlines of the red blood cells in the background. (×1,000.)
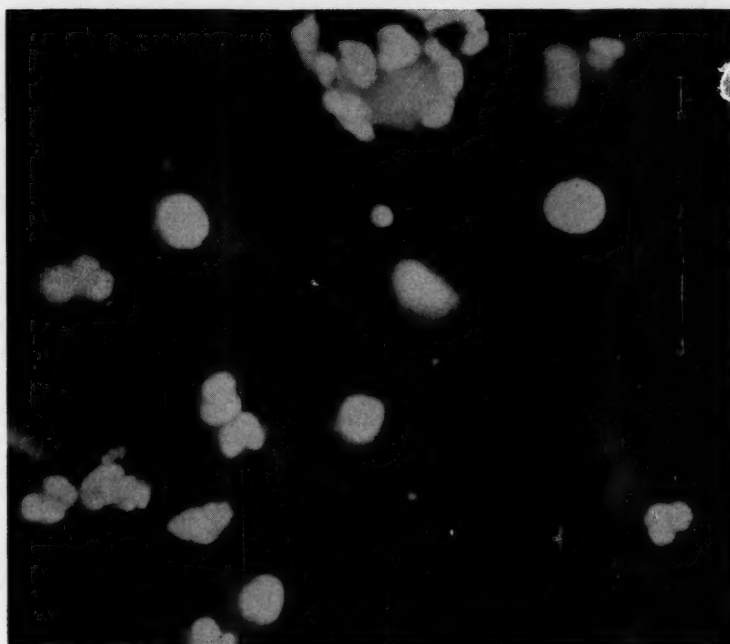
Fig. 4.—Three moderate-sized superficial squamous epithelial cells of angular form from the vaginal smear of a woman during the menopause. The cytoplasm fluoresced dark green while the centrally placed nuclei were green-white in color. Note the brightly fluorescing leucocytes which showed green-white nuclei and reddish-grey cytoplasm. (×1,800.)
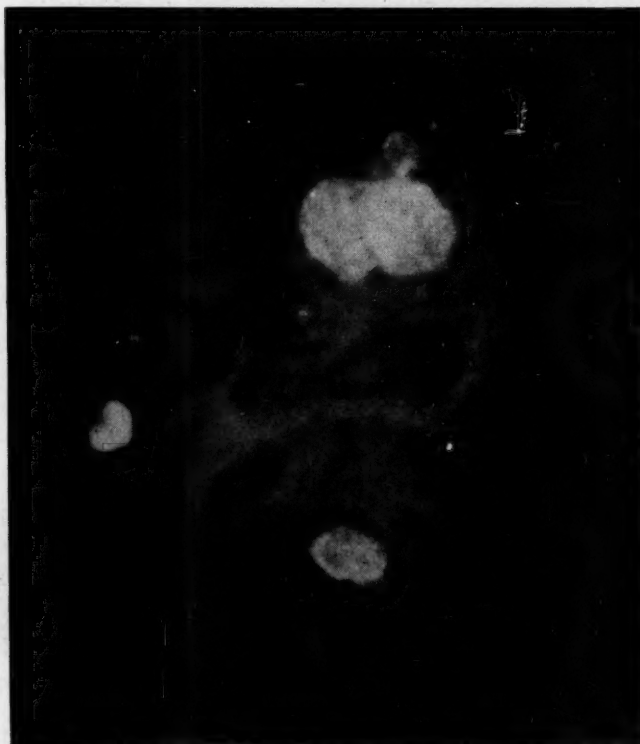
Fig. 5.—The larger of the two cells above is a binucleate malignant cell from a case of epidermoid carcinoma of the cervix. Note the relative small size of the adjacent outer basal-type squamous epithelial cell. The nucleus of the malignant cell was bright yellow which was surrounded by an orange fluorescent zone while the outer border of the cytoplasm was green. Vacuolization of the cells may be seen which is more apparent in the smaller. (×2,000.)
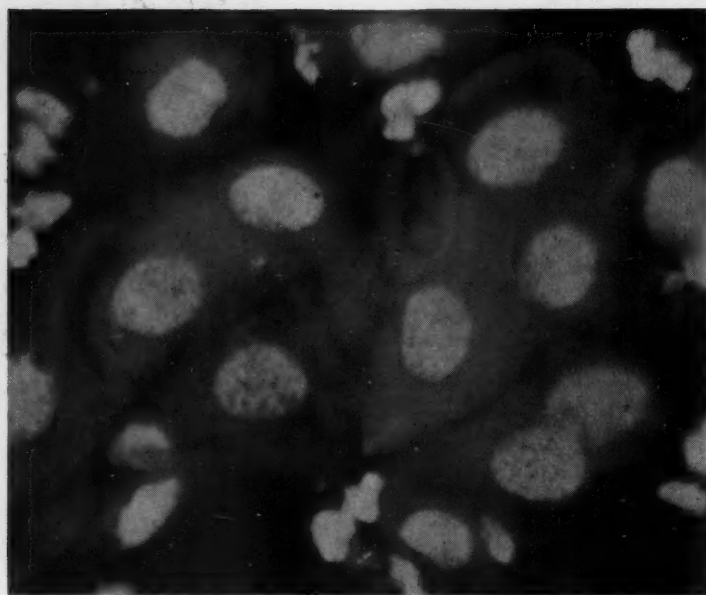
Fig. 6.—Normal inner basal type of squamous epithelial cells. Note uniformity of structure, and the compact, sheetlike arrangement. The relatively large, granular-appearing nuclei fluoresced yellow-white while the cytoplasm showed an orange-brown color. (×2,000.)
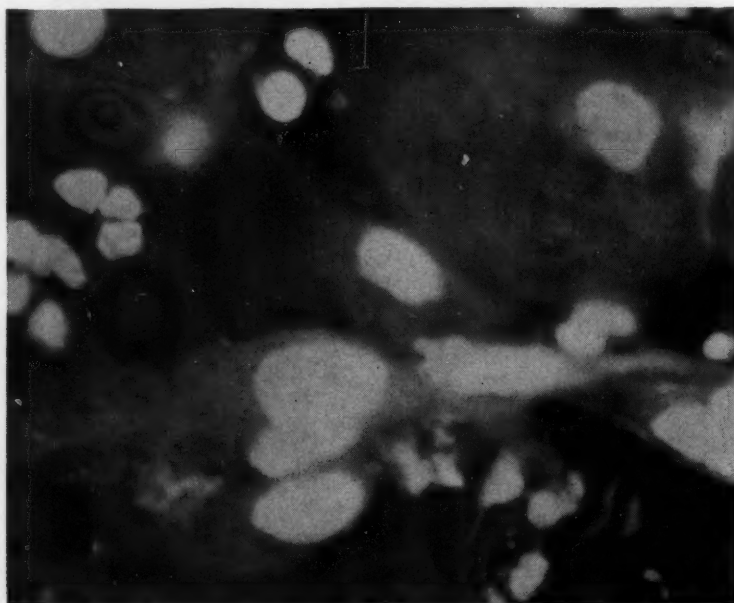
Fig. 7.—In the lower portion of this picture appear six elongated and tadpole-shaped cancer cells from a case of epidermoid carcinoma of the cervix treated with radium six weeks prior to taking this vaginal smear. Note the hyperchromatic, brightly fluorescent, elongated nuclei of the malignant appearing cells which showed a yellow-white color with reddish-orange nucleoli. The degenerating cytoplasm had a bright orange color. Note the outer basal cells above the cancer cells. Several histiocytes may be seen on the left in the middle of the field which had yellow-white nuclei and carmine colored cytoplasm. (×2,000.)

1. Carry slides through 70 per cent and 50 per cent alcohol and distilled water, rinsing five times in each solution.

2. Rinse five times in 0.5 per cent hydrochloric acid followed by five rinsings in distilled water.

3. Rinse five times in acid fuchsin solution (1/2,000), and immediately place in acid fuchsin solution (1/1,000) for four minutes. Rinse five times in distilled water.

4. Place in berberine sulfate solution (1/1,000) for two minutes. Rinse five times in distilled water.

5. Place in acridine yellow solution (1/1,000) for four minutes. Rinse five times in distilled water.

6. Place immediately in a pH 8 buffer solution for forty-five seconds (50 ml. M/5 potassium dihydrogen phosphate; 46.85 ml. M/5 sodium hydroxide; and dilute to 200 ml. with distilled water).

7. Immediately add three drops of ''glycerin compound'' to cover all the stained area on the slide (dissolve 100 mg. berberine sulfate, 200 mg. acid fuchsin, and 100 mg. acridine yellow in a mixture of 100 ml. pH 8 buffer and 400 ml. of glycerin). After three to four minutes, add one drop of berberine sulfate and apply a cover slip. Press firmly between blotters or paper towels to remove excess glycerin. Dip covered slide twice in water to remove glycerin adhering to the cover slip.

8. Seal cover slip by rimming with a saturated solution of isobutylmethacrylate (DuPont), or colorless nail polish.

Fluorescent dyes are photosensitive and should be protected from light when not in use. Distilled water in the staining procedure should be changed after fifty slides have been stained. New dye solutions should be used after staining approximately one hundred slides, or more if the stain continues to be satisfactory. The pH 8 buffer solution should be replaced when it becomes colored a moderately dark yellow-green.

When the stained slide is viewed in ultraviolet light through the ocular of the microscope, the individual cells are seen to fluoresce in various nuclear and cytoplasmic colors against a black background. Areas not stained by fluorochromes appear black since ultraviolet light is invisible. Normal squamous epithelial cells of the inner basal cell type have large yellow-white, round or oval-shaped nuclei surrounded by orange-brown cytoplasm. The intermediate type basal cell has a similar-staining nucleus with reddish-brown cytoplasm containing frequent vacuoles that appear black. Outer basal cells have similar nuclei with greenish-brown cytoplasm. Superficial squamous epithelial cells contain small, pyknotic, greenish-white nuclei, or slightly larger yellow-green nuclei with cytoplasm that in different phases of the menstrual cycle varies from light green to greenish brown. Normal endometrial cells appear singly or in clusters with greenish-gray nuclei and ill-defined, scanty, reddish-brown cytoplasm.

Bacteria of the vaginal flora show either a blue-green or reddish-orange fluorescence. *Trichomonas vaginalis* fluoresces bright orange with a small, central white area when it can be seen. The presence of moniliasis is denoted by very small orange-colored, fusiform-shaped, yeastlike bodies frequently appearing in a chain. Polymorphonuclear leucocytes have bright green nuclei and reddish-grey cytoplasm, and lymphocytes have similar nuclei with maroon-colored cytoplasm. Histiocytes show yellow-green nuclei, usually bean shaped, and bright carmine-colored cytoplasm. Red blood cells are barely visible in a dull lavendar shade, and, accordingly, cause no interfering fluorescence.

Excellent descriptions of malignant cellular morphology appear in the literature.[1, 15] A detailed description of cancer cells stained with fluorescent dyes will be published later. Briefly, malignant cells have a similar fluorescent staining pattern as the type cell from which they are derived, but differ from the normal cell, aside from morphology, in two ways:

1. In general, malignant cells fluoresce more brightly than the normal cell in the same developmental stage. This is possibly due to the well-known increased basophilic tendency of cancer cells, and, accordingly, they are stained quantitatively with larger amounts of the basic fluorochrome, berberine sulfate, which imparts a bright yellow-white fluorescence. Therefore, the hyperchromatic, basophilic nuclei of malignant cells will appear relatively more brightly fluorescent than the normal counterpart. Nucleoli appear a deep orange-red color. Chromatin blocking is clearly visible in the nuclei. Degenerated cells will tend to have grey nuclei and darker cytoplasm.

2. The cytoplasm of most cancer cells will have varying amounts of orange or reddish-orange fluorescence. Normal basal cells, especially the inner basal-cell type, have orange-brown cytoplasm, but in malignant basal-cell types the cytoplasm is a bright orange shade. Large, giant tumor cells frequently have a light orange area circumscribing the brightly fluorescent nucleus whereas this is not seen in normal superficial squamous epithelial cells. It has been observed that cytoplasm associated with adenocarcinoma of the endocervix and endometrial carcinoma cellular components shows a reddish-orange fluorescence. The appearance of any form of orange fluorescence in smaller epithelial cells, endometrial cells, and endocervical glandular cells, or the presence of an orange tint adjacent to the nuclei of large superficial epithelial cells, according to this technique, warrants close inspection under high power magnification. High, dry magnification is satisfactory in most instances ($\times 430$), but oil immersion examination can be carried out with the aid of Shillaber's immersion oil which is essentially nonfluorescent.

In addition to the use of this technique for examining vaginal smears, the same is being utilized for sputum, ascitic fluid, and pleural fluid for malignant cells as well as for a rapid stain for frozen sections which will be reported in a later communication.

Summary

1. A preliminary report of a new technique as a screening method in the detection of uterine cancer is described whereby the cytology of vaginal smears is studied microscopically by staining with fluorescent dyes (fluorochromes) and using filtered ultraviolet light as a source of illumination.

2. The simple and inexpensive apparatus and technique for fluorescence microscopy and fluorescence photomicrography are outlined.

3. Directions for the preparation and staining of vaginal smears are given.

4. Brief descriptions of the various distinguishing fluorescent colors associated with normal epithelial cells, leucocytes, erythrocytes, *Trichomonas vaginalis*, moniliasis, and bacteria of the vaginal flora are mentioned.

5. The use of this technique for differentiating normal from malignant cells by morphology, degree of fluorescent brilliance, and variation of nuclear and cytoplasmic fluorescent colors is cited.

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A CLINICAL EVALUATION OF 3,500 VAGINAL CYTOLOGIC STUDIES

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THE purpose of this study has been to ascertain the clinical effectiveness of vaginal smears in our hands, granting their acceptance by many authors in the larger centers.[5, 6, 7, 8, 9, 12] Because of the interesting data to be set forth below, it is felt that this study may serve as a guide or pattern for other small gynecologic laboratories and clinical services. We will endeavor to answer the question: "How much help can one expect from the vaginal smear as related to the diagnosis of cancer of the female genital organs?" The following material is actually the summation of work done rather than the result of a planned and completely controlled study, and the material for study was thus obtained at random from numerous clinical sources over a period of fifteen months.

Technical Method

Smears were collected, fixed, and stained according to the method advocated by Dr. Papanicolaou,[9] using EA36 instead of the commercially popular EA50, and aqueous alum hematoxylin rather than Harris hematoxylin. Smears were read by two of us (B. W. M. and E. B.), suspicious and positive smears were reviewed and tissue correlated by one of us (N. B. R.).

Clinical Method

All smears reported positive in this study have adequate tissue correlation. Approximately 25 per cent of the negative smears have tissue correlation, the rest having been accepted as clinically benign with the exception of nine cases which will be reported below as false negatives. The term "clinically benign" is derived from clinical follow-up through the private gynecologists and the clinic service, since obtaining tissue from patients who presented merely for a routine check-up and without symptom or sign was not feasible in this large series. This study, however, has been conducted with the aid of competent examiners who have employed other diagnostic techniques in addition to the smear during the pelvic examinations. Each patient in this series has had one or more complete pelvic examinations.

Smears and tissue were obtained and patients were followed from sources representing private outpatient, private hospital, ward outpatient, and ward hospital cases with as many as a dozen gynecologists obtaining the material.

Statistical Method

Smears were classified according to the method of Papanicolaou: Classes I through V.[9] Classes I and II were grouped as negative, Class III as suspicious, and Classes IV and V as positive. For this study, no smears were accepted as proved positive, false positive, or false negative without adequate

tissue confirmation, with the exception of those of two patients, now dead, who had known carcinomas with vaginal stenosis.

For the purposes of this report, the 3,500 cases do not include any Class III (suspicious) smears, since they represent a unique problem, to be discussed in a subsequent paper in detail.

Data and Discussion

The findings of the 3,500 vaginal smears are as set forth below:

Smears reported Class I or II	3,407 or 97.4%
Smears finally proved benign	3,415 or 97.6%
Smears reported Class IV or V	83 or 2.6%
Smears finally proved malignant	85 or 2.4%
Total	3,500

It will be noted that 3,407 smears were classified as negative and ninety-three as positive, whereas after complete clinical and/or tissue study 3,415 cases were accepted as benign and eighty-five as malignant, giving an over-all incidence of malignancy in this series of 2.4 per cent.

The clinical evaluation and analysis of error of smears reported are as set forth in Table I.

TABLE I. BREAKDOWN OF ERROR

TYPE OF CARCINOMA	NUMBER OF CASES CALLED CARCINOMA BY SMEAR	NUMBER OF FALSE POSITIVE SMEARS	NUMBER OF CASES PROVED MALIGNANT	NUMBER OF FALSE NEGATIVE SMEARS	TOTAL NUMBER OF ERRORS BY SMEARS IN 3,500 CASES
Adenocarcinoma	19	6 (31.6%)	18	5 (27.8%)	
Squamous carcinoma	74	11 (14.9%)	67	4 (5.9%)	
Total of all types	93	17 (18.4%)	85	9 (10.6%)	26 (0.74%)

It will here be noted that there was a total of ninety-three cases called positive by smears, of which seventeen were subsequently placed in a false positive category by failure to recover malignant tissue. Of the 3,407 smears reported as negative, nine patients were found to have malignancy. Thus the total number of errors for the entire series of 3,500 vaginal smears was twenty-six or 0.74 per cent.

This error, although a conventional means of expression in use by several authors,[5, 8, 9, 12] falls far short of portraying the true effectiveness of vaginal smears in clinical gynecology. The figure is misleading and is not the one which a physician may offer any given individual. To show the inadequacy of expressing the percentage of error on a basis of negative cases, where these run better than 97 per cent of the total (thus acting as a diluent for error), the subsequent data are computed on the basis of malignant cases irrespective of the number of negative cases in the series. *It thus sets forth the efficacy of vaginal smears to any given patient were this patient to harbor a malignancy.*

By reference to Table I, it will be seen that there were nine false negative smears out of eighty-five clinically proved carcinomas, representing an 11 per cent error. This indicates that if a patient has a genital tract cancer, the vaginal smear has an 89 per cent chance of picking it up; on the other hand, seventeen false positives out of ninety-three smears called positive means that any given patient with a positive smear has an 82 per cent chance of harboring cancer, and an 18 per cent chance of having a benign lesion. This fact

Fig. 1.
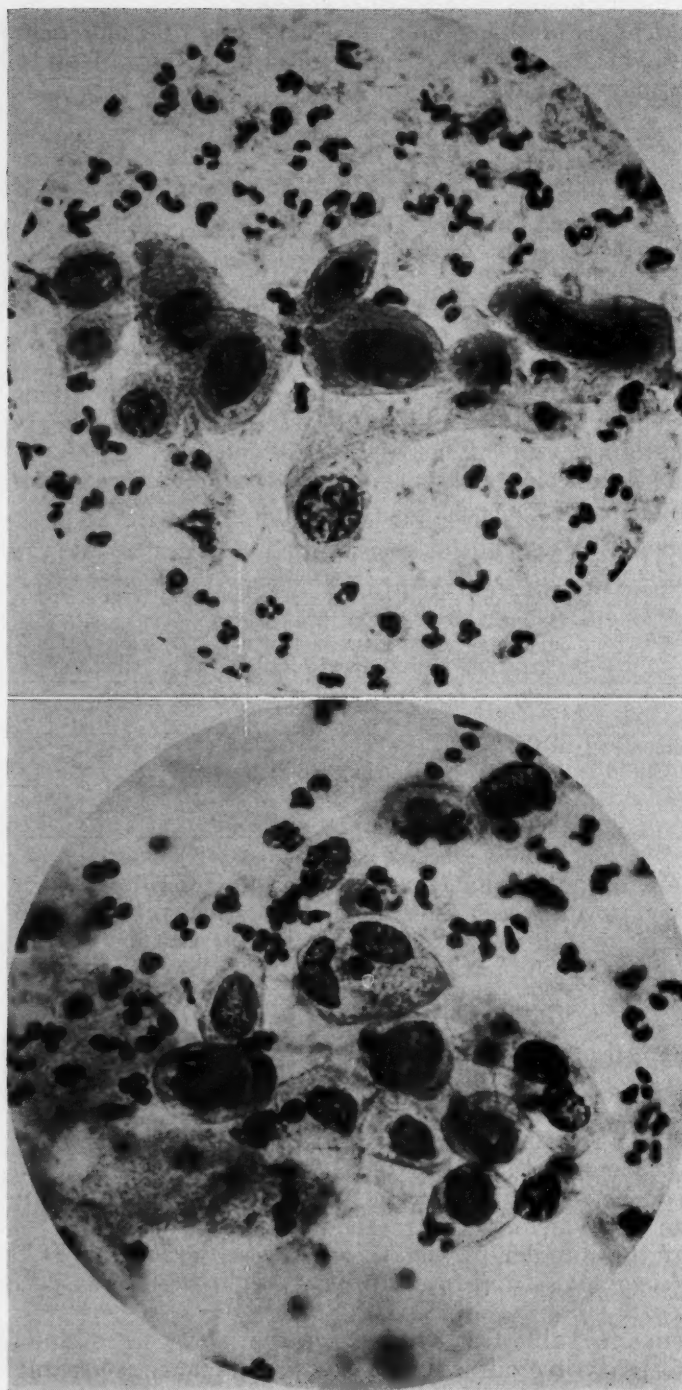
Fig. 2.

Fig. 1.—Well-differentiated invasive squamous carcinoma of the cervix. Compare with Fig. 2 below. Smear report: Class V. (×650.)

Fig. 2.—Trichomonas vaginalis infestation. These cells disappeared and the smear became normal after treatment of the infection. Smear report: Class III. (×650.)

Fig. 3.
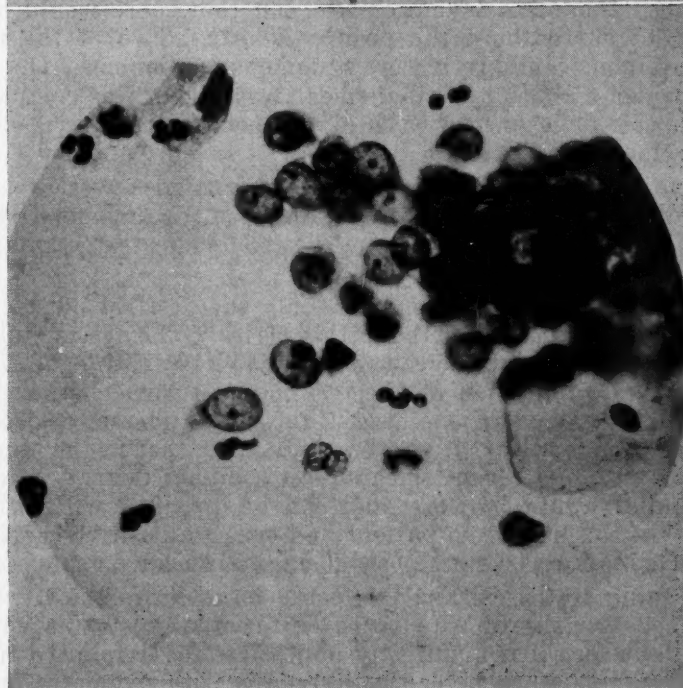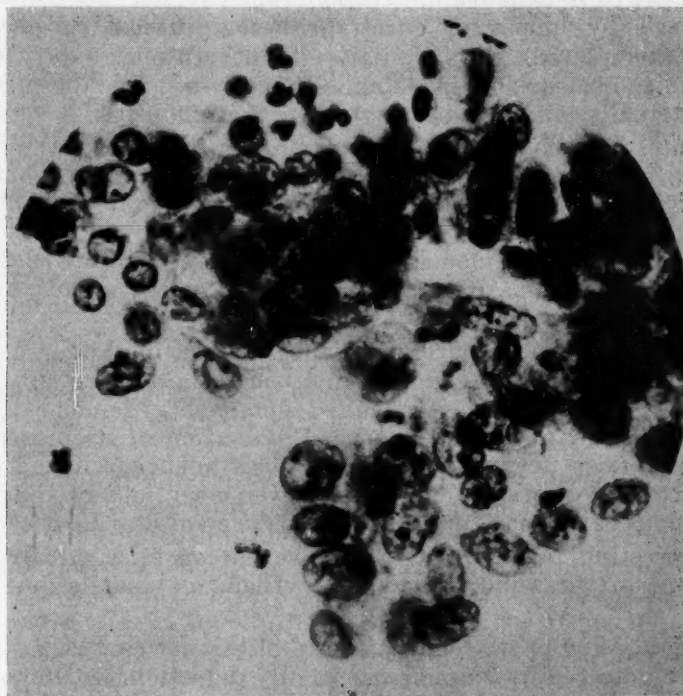
Fig. 4.

Fig. 3.—Infiltrating adenocarcinoma of the endometrium. Note the piling of cells and macronucleoli. Compare with Fig. 4 below. Smear report: Class V. (×650.)

Fig. 4.—Stripped nuclei of endocervical cells, normal. (This smear taken after pelvic examination.) The prominent nucleoli and the piling of cells caused an erroneous report of adenocarcinoma: Class IV. (×650.)

alone places a grave responsibility upon the clinician to confirm a positive smear diagnosis by biopsy or curettage before radical surgery or radium therapy is contemplated. It is similarly the practitioner's duty to use means in addition to the smear for the establishment of a pelvic diagnosis, since the smear alone actually misses 11 per cent of the malignancies.

The greatest source of error in the malignant category was derived from endometrium, since we failed to diagnose adenocarcinoma when present in five out of eighteen cases, and incorrectly thought it to be present in six cases which subsequently presented benign endometrial lesions. On the basis of eighteen proved adenocarcinomas in this series, the error was 27.8 per cent false negatives. On a basis of nineteen cases called adenocarcinomas, six cases, or 31.6 per cent, proved to be false positives.

Diagnosis of squamous carcinoma shows a much greater accuracy than does adenocarcinoma of the endometrium, since there were only eleven false positives out of seventy-four cases called squamous carcinoma by smears for a false positive error of 14.9 per cent. Elimination of its presence also presents a smaller false negative error than does adenocarcinoma of the endometrium, since there were four false negative smears out of sixty-seven cases proved squamous carcinoma for a false negative error of 5.9 per cent.

It is interesting to note that of the seventeen false positive smears obtained, not one of these individuals was without evident lesion, however benign.

Of the eighty-five proved malignancies in this series, twenty cases, or 23.5 per cent, were detected by vaginal smear. By detection, we do not necessarily mean that the patient was asymptomatic, but that there would have been no immediate follow-up without the positive smear. Two of the twenty cases were adenocarcinomas, eighteen were squamous carcinomas. One of these patients, from whom a routine vaginal smear was taken, was completely asymptomatic. Biopsies done on the basis of the positive smear report revealed a squamous carcinoma in situ of the cervix.

Seventeen of the eighty-five proved malignancies were recurrent cases following radiation therapy. Of these, thirteen, or 76.5 per cent, were detected by smear. This very gratifying figure demonstrates another valuable use of the vaginal smear.[4]

For the sake of statistical analysis, only the first set of smears obtained from any patient was considered for this series. The set includes a vaginal smear, a cervical smear, and a cervical surface biopsy using the Ayre spatula.[1] On actual clinical application of the technique in some instances several repeat smears were taken. In one case, a false negative smear was followed a few days later by a frank positive, thus indicating that in the clinical application of vaginal cytology repeat smears offer a higher degree of accuracy than controlled studies would indicate, and can be obtained with little or no inconvenience. In this study, no patient had either a positive cervical smear or cervical surface biopsy without a positive vaginal smear.

The foregoing statistical analysis could be made to show even less error on the false negative side if we eliminated terminal postradiation carcinomas and other cases where it is manifestly impossible for exfoliated tumor cells to appear in the vagina, such as cervical stenosis with pyometra and adenocarcinoma. Two patients died of extensive pelvic carcinoma without a residual local lesion. One patient, treated with radium many years ago for adenocarcinoma of the endometrium, developed complete cervical stenosis along with adenocarcinoma and a rhabdomyosarcoma of the uterus. In fairness to the vaginal smear technique, these errors should not be considered to detract

from the general clinical value of the procedure, any more than the absence of carcinoma in a biopsy would invalidate this procedure because of poor sampling or inaccessibility of the lesion.

In the same light, improperly taken smears or smears taken following a douche or vaginal examination, yielding false negative results should not be charged against the accuracy of vaginal cytology. For the purpose of this statistical study, however, no allowance has been made for this. A notable example is a patient with squamous carcinoma of the cervix in whom the pipette was inserted for only a few centimeters. Because of a positive biopsy, a properly taken repeat smear was examined, revealing large quantities of tumor cells.

In this series only one of the nine false negative smears has by re-examination of the initial smear revealed any atypical cells sugestive of carcinoma. This smear was from a patient with a bizarre acanthoma of the endometrium containing unusual cells. The cells in the smear closely resembled those in the curettings from this patient and those found in a distant metastatic focus. Were such cells to be seen again, it is not unlikely that the same false negative error would be made.

As experience was gained with the use of the cytologic method for cancer diagnosis it became more apparent that experience plus thorough training under recognized authorities is the sine qua non for interpretation of all but the clear-cut negatives and positives. Radiation cases, cases with benign endometrial lesions, chronic cervicitis with atypical hyperplasia, and trichomonas infestations offer pitfalls for false positive error primarily.[3, 11]

The accompanying photomicrographs illustrate a few of the diagnostic errors which were overcome through experience.

Summary

1. Analysis has been made of 3,500 vaginal cytologic studies and of the clinical and/or tissue follow-up of these cases. Eighty-five cases of carcinoma of the uterus, cervix, vagina, or vulva were discovered.

2. In eighteen cases of adenocarcinoma there were thirteen positive smears and five negative, yielding a false negative error of 27.8 per cent. In addition, six smears were mistakenly called adenocarcinoma for a false positive error of 31.6 per cent. In sixty-seven cases of squamous carcinoma, there were four false negative smears, giving a false negative error of 5.9 per cent, and there were eleven false positive smears with an error of 14.9 per cent.

3. In all, nine smears were erroneously called negative for a total negative error of 10.6 per cent. On the other hand, seventeen smears called positive were proved incorrect for a total false positive error of 18.4 per cent. The combined error for the entire series is thus twenty-six out of 3,500 cases, or 0.74 per cent.

4. An attempt has been made to show that the statistical picture presenting the results of a controlled study of vaginal smears often falls far short of representing the true value of the technique to the clinician and the patient.

Conclusions

Based upon the clinical evaluation of 3,500 vaginal cytologic studies and the experience of others obtained from the literature, the Department of Gynecology is of the opinion that the vaginal smear is a valuable adjunct in the di-

agnosis of pelvic disease. It is helpful both in the malignant and nonmalig-
nant aspects, but it in no way has come to be used as a substitute for the rou-
tine pelvic examination, biopsies, and curettage when indicated. The follow-
up of postradiation malignancies appears to be another value of the vaginal
smear, as well as the occasional incidental detection of a carcinoma in an
otherwise clinically benign case. To the present writing, the vaginal smear
has not been, and will not be the basis for gynecologic surgery, or the reason for
not employing surgery until all other diagnostic criteria have been met.

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PSYCHOSOMATIC ASPECTS OF STERILITY

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THE declining birth rate in all countries of the Western world is indicative of its declining psychic health and is, in general, a morbid manifestation of the process of social disintegration that is taking place. Lorimer and Osborn,[1] who have investigated most extensively the various explanations for the declining birth rate, summarize as follows: Involuntary sterility and limited fecundity are important factors in determining reproductive rates, but recent conspicuous changes in birth rates must be attributed to social factors. Lundberg and Farnham[2] say that with the change of a word—social to emotional—they would be in complete agreement. Pseudo sterility due to birth control, and psychogenic sterility, known to occur in some women, may be the end result of a deep-seated neurotic anxiety pervading our culture. The latter types of sterility actually represent the complete failure of normal female biological functioning. Psychogenic sterility probably occurs far more often in civilized rather than primitive peoples.

Present-day clinical medicine has made tremendous strides in improving the public health, but up to the present time the problem of psychogenic sterility and infertility has received relatively scant attention. Dickinson[3] correctly observed, ''The psychology of infertility, voluntary or involuntary, is as important as that of excessive multiparity.'' The theory that conception is subject to psychological influences is not new, but should be more thoroughly investigated now because of the increasing attention clinicians are giving to the fruitful field of psychosomatic research. Ancient primitive peoeple successfully used incantations and religious rituals to alleviate the sterile state, yet until recently few gynecologists seriously considered psychological influences as a factor in sterility in spite of the fact that the fertility of schizophrenics and epileptics is diminished by about 50 per cent.[4]

There is an increasing literature which assigns considerable importance to the mental state and the unconscious wishes of the patient.[5, 6, 7, 8] Thus, some physicians,[9, 10] especially psychiatrists, have written on the subject of psychogenic sterility, the basis of their remarks being limited to observations concerning childless couples who conceived after the adoption of a child and reference to patients who conceived following psychoanalysis.

Calverton and Schmalhausen[11] and others[12, 13] have also considered as evidence of psychogenic sterility their experiences with frigid women who were also sterile, but became pregnant following successful treatment of their frigidity. These assumptions from a scientific standpoint are most inconclusive and should be challenged from a statistical standpoint. The incidence of frigidity is notoriously high in the Western world, and a very great percentage of these orgastically impotent women are able to bear children. Until statistics are presented showing a higher incidence of sterility in frigid women, these claims must also be challenged.

Unfortunately, there is complete lack of controlled evidence regarding the mechanism of psychogenic sterility. Various theories regarding the hypothalamic[14, 15] and pineal[16] influences on the anterior pituitary gland causing changes in ovarian function and ovulation have been postulated. These neuroendocrine changes as etiological factors have been considered by many investigators.[17-24] True psychogenic sterility presupposes an absence of demonstrable endocrine dysfunctions which can rather readily be detected by methods now available. De Lee[25] thought that psychogenic sterility was due to "agenesis of the anlage," referring to the failure of the biologically inherited mental and constitutional factors of the individual. This type of sterility may also be secondary to some form of tissue incompatibility, i.e., a low response to estrogens,[25a] or local anaphylaxis. Rommer[26] considered the psyche in relation to sterility under two broad classifications: psychogenic sterility and neurogenic sterility. He observed that allergy and associated conditions may cause sterility by inducing an edema of the cervix and endometrium. These statements may be true, but we know little about such etiological factors in sterility.

At this point we wish to call attention to one possible alteration in the female generative organs which may account in a relatively simple manner for psychogenic sterility. Constriction of the smooth muscle at the uterotubal or isthmotubal junction may occur in these individuals,[26] thus preventing the ovum from meeting the sperm in the tube. Stallworthy[27] feels that uterine irritability is a manifestation of autonomic dysharmony and is the most common cause for the erroneous diagnosis of tubal occlusion. The false diagnosis of tubal blockage due to spasm may be made frequently in hypertonic individuals even after gas insufflation or Lipiodol radiography. He has definitely observed this spasm of the uterotubal junction under fluoroscopy and believes that the most common cause for uterotubal blockage is the lack of synchronization of the waves of contraction which he has seen originating at the uterine cornua. We, too, believe that this uterine irritability, with tubal dyskinesia and blockage, may be a relatively permanent condition in tense individuals and is the basis for one of the principal psychosomatic factors in causing not only psychogenic sterility, but may also account for ectopic pregnancy as well! This is not inconceivable when it is realized that autonomic imbalance is seen in the production of bronchial, gastrointestinal, and bladder spasm. These are more or less permanent conditions in certain nervous and tense individuals.

Such a possibility of tubal spasm would account for the normal endocrine findings associated with this type of sterility. Evidence to substantiate this concept is the well-recognized psychological fact that spasm of the smooth muscle is one of the most common visceral responses to emotional tension. This response of uterotubal spasm to emotional tension in such individuals may not even be relieved by anesthesia. Also the fact that the inner one-third of the tubes is innervated by nerves from the hypogastric plexus is consonant with the effect of the sympathetic stimulation that is so intimately concerned with the emotions. For years it has been commonly known that spasm or relaxation of the Fallopian tubes is seen at the uterotubal or isthmotubal portion in tense and anxious individuals during tubal insufflation.[28] The administration of atropine or other spasmolytic drugs is known to relax the spasm. Furthermore, in testing for tubal patency, it has been demonstrated that the premenstrual period is one of

great stress and tension in most sterile women and greater pressure is required to overcome the resistance of the uterotubal junction. The spastic tubes may even be sufficiently patent to permit the passage of carbon dioxide under high pressure and yet insufficiently patent during spasm, due to nervous stimuli, to permit the passage of the ovum, the largest cell in the human body.

The method by which the unfertilized and nonmotile ovum makes its way down the tube has not yet been established. The general conception is that it is urged along by peristalsis-like movement of the tube and its cilia. Such movements may also be subject to functional impairment or dyskinesia due to psychic imbalance. Stallworthy states,[27] "The female genital tract is the most 'hysterical' portion of a woman's anatomy. It is under both a nervous and hormonal control, a fact which is sometimes forgotten in these days of hormonal emphasis. . . . In our search for stronger and better hormones I fear we have somewhat neglected the role of the autonomic nervous system in maintaining the harmony of the genital tract."

The following history illustrates how the erroneous diagnosis of tubal blockage may be made in a tense and nervous individual:

Gabrielianz[29] reported the case of a patient, aged 31 years, by profession a ballerina, with a history of sterility, who had been married five years and had never become pregnant. Menstruation began at 13 years, regular, four-week type, three to four days in duration. She had occasional dysmenorrhea of a few hours' duration on the first day. Her past history was negative, both medically and surgically. She was subject to *nervous tension* and *unbalanced emotions*.

Clinical examination revealed no pathologic findings. On examination, the uterus was in normal anteflexion, slightly enlarged, of normal consistency, symmetrical, freely movable, and not tender. The adnexa were not palpable.

The examination of the husband's seminal fluid, performed within one hour after intercourse, showed the spermatozoa in abundance, vigorously motile, with normal length of tails and normally shaped heads.

Following this examination a hysterosalpingography was performed on the wife; 9 c.c. of Lipiodol were used. After injection of 8 c.c. the patient complained of pain in the uterine region. One more cubic centimeter was added before taking the pictures. One cubic centimeter of iodized oil is sufficient to fill up the tubes and pass through the fimbriated end of the tubes. The spill is moderate in amount and gives the possibility of correct interpretation.

Five minutes later the second x-ray picture was taken. The last picture was taken after twenty-four hours. The first picture showed the right tube patent, the upper third of the left tube was visualized. On the second picture there was slight visualization in the proximal end of the right tube; visualization in the left tube was the same. The last picture showed no evidence of oil in the pelvis.

From the pictures, he felt that pregnancy was unlikely. Because of the findings on hysterosalpingography, he told her that contraceptives would not be necessary.

The patient left the city but reported by letter that she had only one menstrual period, one month later, and that for the first two months she danced without realizing that she was pregnant, feeling well all the time. He was later informed that the patient had delivered a baby girl eleven months after the Lipiodol visualization.

Gabrielianz concluded that the iodized oil in the left tube passed into the abdominal cavity, perhaps straightening out the kink or relieving some other obstruction in the tube.

We disagree with his conclusion that the iodized oil later passed through the tube and rendered it patent. It is possible that this patient, because of the physician's advice, became psychologically relieved of the subconscious fear that pregnancy would inter-

fere with her dancing. As a result, the tubal spasm, which no doubt accounted for the incorrect interpretation, was relieved. Also, the insufflation was performed just before her expected menses when the patient's nervous tension would be exaggerated. This case illustrates that our present theories concerning tubal occlusion, even when diagnosed radiologically, need clarification before a supposedly sterile patient is told that she cannot become pregnant.

Another factor accounting for psychogenic sterility is the possibility that disturbed emotional states may adversely alter the specific chemical and physical properties of the secretions in contact with the sperm and ovum, just as anxiety modifies salivary and gastric secretions. Taylor[29a] has described a gynecological syndrome accounting for relative sterility, due to "congestion-fibrosis," the result of long-standing hyperemia and congestion of the tubes and ovaries, to a great extent dependent on conscious or unconscious stimuli. While these speculations are attractive, we still lack sufficient data for reliable evidence. These observations are presented to stimulate search for the physiological alterations of the sexual apparatus under the influence of psychogenic factors.

Psychodynamic Factors

It is claimed that women who are sterile but endocrinologically normal have chronic anxieties, including the fear of pregnancy, which are psychologically repressed and of which they themselves are often unaware. Another interesting theory presupposes that many women are unconsciously aware of the time of ovulation. This, combined, with fears of pregnancy, causes some women to refrain from coitus during ovulation with resultant infertility. The fact that many sterile women are consciously eager to get pregnant and are bitterly disappointed by their inability to do so does not rule out the hypothesis that in some women their unconscious wishes against pregnancy may predominate. Also present in these patients are infantile emotional attitudes wherein the wife's unconsciously assumed father-daughter relationship would be upset by pregnancy. Another type is the dominant wife who repudiates femininity and assumes a masculine role which pregnancy and motherhood would destroy. Deep-seated hostility may also be a primary factor in psychogenic sterility with one mate and not with another. It may be possible that unconscious psychic disorders and conflicts make pregnancy undesirable and unpleasant. Since these same psychic factors may produce other visceral changes, one can assume that these women are susceptible to this particular emotional reaction.

According to Deutsch,[30a] the endocrine system of the female reproductive apparatus "complies" with the content of emotional conflicts. She has commonly seen pregnancy follow renunciation of a career. As the result of greater readiness for motherhood, emotional factors conducive to pregnancy may ensue. This mechanism may be similar to the tremendous increase in maternal feelings observed following the adoption of a child. Another factor considered by Deutsch in psychogenic sterility is that paradoxically the change of living conditions for the worse, even painful, brings fulfillment of pregnancy to many women. She thinks that expiation of old guilt feelings through suffering and sacrifice sometimes relieves inner tensions. She also believes that the physical treatment used by gynecologists to treat sterility may actually play the part of liberating punishment and it is this factor which is often of primary importance in achieving results.

The psychodynamics of the hypothesis of uterotubal spasm as a specific etiological factor responsible for psychogenic sterility may be better understood by the fact that stimuli from without or from within the body initiate a state of

genital tension. This state of tension seeks a motor or secretory discharge in order to bring about relaxation. Therefore, opposing forces are at work in disturbed individuals and their strength depends upon the patients' unconscious desires. The evaluation of these inhibiting forces, and of their origin, and their effect on the discharge of nervous stimuli is necessary before psychogenic sterility can be completely understood and treated.

The following case history demonstrates some of the above psychological mechanisms:

Mrs. B. M., aged 28 years, gravida 0, para 0, had a history of sterility of seven years' duration. Physical examination and a complete sterility work-up of both partners revealed no pathology. The husband had a 15-year-old son by a previous marriage. The past history of the wife was essentially negative except for a ventral-fixation operation performed four years before for a retroverted uterus. The surgeon indicated that the correction of the condition might result in pregnancy. Following a wide variety of hormonal therapy the patient still failed to become pregnant. The patient was asthenic and rather immature with poorly developed secondary sexual characteristics. Many lesions were present on the buccal surfaces of both cheeks. She stated that she had consulted several physicians about these lesions without obtaining relief. The following psychamnestic details were elicited: She was extremely nervous, easily fatigued, and felt ''generally run down.'' She married her husband, who was 23 years her senior, because ''he had such beautiful white hair'' and he was everything that her father should have been. Intercourse was gratifying as evidenced by her having vaginal orgasms most of the time. She stated that she sincerely wished to have a child of her own even though she was now taking care of her stepson. Because of her negative gynecological findings, her history of nervousness, tension (manifested by the self-induced lesions of her mouth by unconscious biting), and childlike appearance it was felt that this was a possible case of functional sterility. Brief psychotherapy consisting of assurance, explanation, and ventilation of the patient's thoughts was employed.

A superficial exploration revealed the following pertinent material: She realized that her relationship to her husband was obviously that of a daughter to a father. As a child she had always felt rejected by her own father. She had always been rather frail and ''sickly.'' Her mother had always been solicitous for her welfare. Because of her ailing and complaining nature, she was able to gain attention and get things that she wanted. Her husband was extremely sympathetic and always ''babied'' her. It was felt that the lesions in her mouth were probably the result of her tension and present nervousness. The patient was given insight into her unconsciously assumed father-daughter relationship, which she now recognized. She was instructed to keep an accurate temperature record and to have intercourse when ovulation occurred. She was told that there was no reason why she could not get pregnant if the insight gained as a result of her psychotherapeutic interviews was accepted. The patient felt greatly relieved and six months later reported that she was pregnant. She delivered a normal infant at term. Following the successful outcome of her pregnancy there was a marked diminution in her nervousness and the lesions in her cheeks improved.

The subsequent history was as follows: The patient made a normal adjustment to her maternal role and apparently was very happy. Four years later the patient returned pregnant again. She was now extremely nervous because her husband was drinking excessively. About one year after the birth of her first baby she became frigid. This was presumably based upon her husband's impotence, which also began at this time. At two and one-half months' gestation she aborted, in spite of bedrest and empirical treatment.

Of course it is difficult to assume with certainty that this patient conceived because of psychotherapy. However, in view of her past history one may deduce that the release from psychological tension may have been a factor in her conceiving. The psychodynamic factors present in this patient indicated an unconscious father-daughter relationship which was disturbed by her first pregnancy. The adoption of the maternal role displaced love

from her husband to her child, resulting in unconscious hostility for her husband; which no doubt was due to the recognition of the disturbed father-daughter relationship. The birth of the baby served as a specific stimulus that this relationship no longer existed. The unconscious hostility was expressed in her total frigidity. These factors were sufficient to produce an emotional upset and no doubt accounted for the abortion. Stallworthy has shown that this type of patient has an autonomic instability so great that minimal stimuli may provoke an extreme response when uterine irritability is present. We may further assume that because of this patient's emotional tension she aborted when subjected to stress that exceeded her tolerance.

Diagnosis

The diagnosis of psychogenic sterility is based on a failure to conceive after both partners have been proved to have normal reproductive organs. Every sterile woman should have a complete physical and endocrinologic survey. Tubal insufflation and radiography should be supplemented by a detailed study of the uterus and tubes under fluoroscopy. This is best performed under Pentothal Sodium or hypnosis, since in this state nervous stimuli are minimal. If all possible anatomic and endocrine disturbances are ruled out, the patient should be seen by a psychiatrist or by a psychiatrically orientated gynecologist. A careful anamnesis of her entire life situation, along with its specific conscious and unconscious conflicts, should be ascertained. Faulty attitudes toward psychosexual functioning should be corrected. Realization that psychic and somatic manifestations are different aspects of the sum total of the whole personality may offer further information to the therapist.

Wittkower and Wilson[30] have made some interesting studies of the personality in cases of psychogenic sterility. The patients appeared to be much more poorly adjusted psychosexually than a control group. The sterility patients were characterized by juvenile facies and physiques, withdrawn personalities as children, parental overprotection, inferiority feelings, the desire to remain childlike, and the grasping for sympathy and affection. Psychological projective tests, such as the Rorschach and Thematic Apperception Tests are useful as diagnostic methods in this respect. These tests are tremendous time savers and are valuable indices to the structure of the whole personality and aids in the disclosure of some of the psychodynamic factors discussed above.

Treatment

Since reproduction is the principal drive and life goal of the woman, prophylactic treatment should begin before the menarche or even in early puberty if possible. It is believed that preconceptional care will play a most important role in this condition. This will bring about the proper maturation so that the reproductive stage will be reached in the best possible physiological potency. This will consist of universal sex enlightenment, correction of faulty attitudes toward pregnancy, improved interpersonal relationships with parents, siblings, and persons close to the little girl. Bear[31] emphasizes this when he states, "This preventive aspect of the management of human sterility not only involves the work of the physician, but also extends into the field of economics, of sociology, and education." Such a psychological approach involves therapeutic measures that will have a more far-reaching effect on the patient.

It is also advisable to treat sterile women when they are younger, since their normal physiological capacity for pregnancy diminishes as they grow older.

Endocrine therapy is unsatisfactory in psychogenic sterility. Androgens have been known to abolish the spasm of the uterotubal junction and reduce

the associated hypertonicity to normal.[32]   All cases should be adequately controlled, since 35 per cent of all sterility patients will become pregnant regardless of the therapy used.

It has been frequently observed that tubal insufflation has brought about pregnancy.   This may possibly be due to the mechanical relaxation of the tubal spasm which we think is present in these cases.   Rubin[33] thinks that a possible psychosomatic effect cannot be ignored when uterotubal insufflation is performed.   In his opinion, although actual tubal obstruction is not encountered, sometimes the mere performance of tubal insufflation may serve as an intense emotional stimulus which relaxes the tubal and cervical sphincters, while possibly provoking ovulation in a manner analogous to that which takes place in lower animals.   This is a highly speculative hypothesis.   Vollmer[26a] found that, when the tubal spasm was prevented by sedatives (women practically asleep during intercourse), pregnancy resulted.

In regard to psychotherapy, this, of course, depends on the patient's total method of reaction to anxiety and tension.   Since the sources of the disturbance go so far back into the patient's life, it can hardly be expected that they can be uprooted in a few therapeutic sessions.   A complete release from chronic anxiety and tension may take many months of psychotherapy or therapy psychosomatically orientated.

Such psychotherapy consists in allowing the patient to ventilate her repressed feelings, thus making possible the therapist's recognition of the psychodynamic factors responsible.   Close attention, patience, and personal interest by the physician will be extremely helpful in establishing a closer rapport.   No patient should be told, "There is no reason why you can't get pregnant."   In all such cases reassurance is an important adjunct to psychotherapy.   This is especially true where the anxiety and tension are so severe and overwhelming that the patient seems to be depressed because of her inability to conceive.   Reassurance will provide support and act as a buffer to the repeated irritations of a disturbed personality and thus greatly facilitate therapy.   Even normally functioning patients, subject to occasional neurotic anxiety attacks, will benefit from reassurance.   Even such simple reassurance as telling the patient, "Nothing is wrong in any way, so now all you need to do is go on home and get pregnant," has helped to bring on pregnancy in tense individuals.[34]

In refractory cases, deeper psychosomatic therapy is necessary to determine the mechanism and production of these patients' specific conflicts and neurotic disorders.

Summary

Psychogenic sterility should receive more attention from clinicians because it is well recognized that emotional conflicts can produce somatic dysfunctions in the generative organs.   We believe that autonomic imbalance produces tubal spasm which may be a relatively permanent condition in tense and nervous individuals, thus accounting for this type of sterility.   A careful psychanamnesis, together with a physical examination consisting of direct visualization of tubes, should be made in all cases of sterility.   With adequate study, the relationships between emotional states and sterility may cast a different light on this age-old problem.   Personality studies, together with psychological tests, are helpful in establishing the diagnosis of psychogenic sterility.

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METACHROMASIA IN THE ENDOMETRIUM

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THE recent demonstration of the physiologic importance of certain acid mucopolysaccharides in tissues has produced increasing interest in these substances. The physiologic and chemical nature of heparin and hyaluronic acid in particular have been studied extensively (Jorpes,[1] Meyer[2]). It has been shown that metachromasia is one of the properties of these substances and that they may be demonstrated in tissues as a result of this property (Wislocki, Bunting, and Dempsey[3]). Several authors have reported the presence of metachromatic substances in human endometrium and decidua (Bensley,[4] Dempsey and Wislocki,[9] Sylven[5]). It is the purpose of this paper to describe the changes in the metachromatic substances in the endometrium during the menstrual cycle and in hyperplasia and carcinoma of the endometrium.

Materials and Methods

A group of thirty-eight specimens of endometrium were obtained from uteri removed surgically for various reasons.* The tissues were fixed in a 4 per cent solution of basic, lead acetate for twenty-four hours. The deparaffinized sections were stained in a 0.5 per cent aqueous solution of toluidine blue, according to the methods of Holmgren and Wilander[6] and Holmgren.[7] Alternate sections were incubated for eighteen hours in hyaluronidase since Wislocki, Bunting, and Dempsey[3] have shown that metachromasia due to the presence of hyaluronic acid may be abolished by such treatment.†

The stage of development of each nonpathologic endometrial sample was determined according to the method of Hertig.[8]

Twelve of the normal endometria were of the proliferative type and twenty were of the secretory type. One example of fifteen-day endometrium was examined. The date of this endometrium was determined by the fact that there was a recently ruptured follicle in the ovary which showed early luteinization, yet the endometrium did not show evidence of secretion and presented the histologic picture of late proliferative endometrium. Among the secretory endometria were examples of all stages of development up to menstruation. One specimen of endometrium of early pregnancy, three examples of cystic hyperplasia, and one example of secretory hyperplasia were studied, in addition to two cases of adenocarcinoma of the endometrium.

According to Wislocki and Dempsey[9] metachromasia in tissues following this method is principally due to mucopolysaccharides. However, in some instances it may be attributed to ribonucleoprotein and in some locations the chemical nature of the substance producing metachromasia is unknown.

Results

Proliferative Endometrium.—Metachromasia was present in the intercellular spaces of the stroma of the endometrium in all specimens of this stage of development (Fig. 1). It was present in the superficial one-half or two-thirds

Fig. 1.
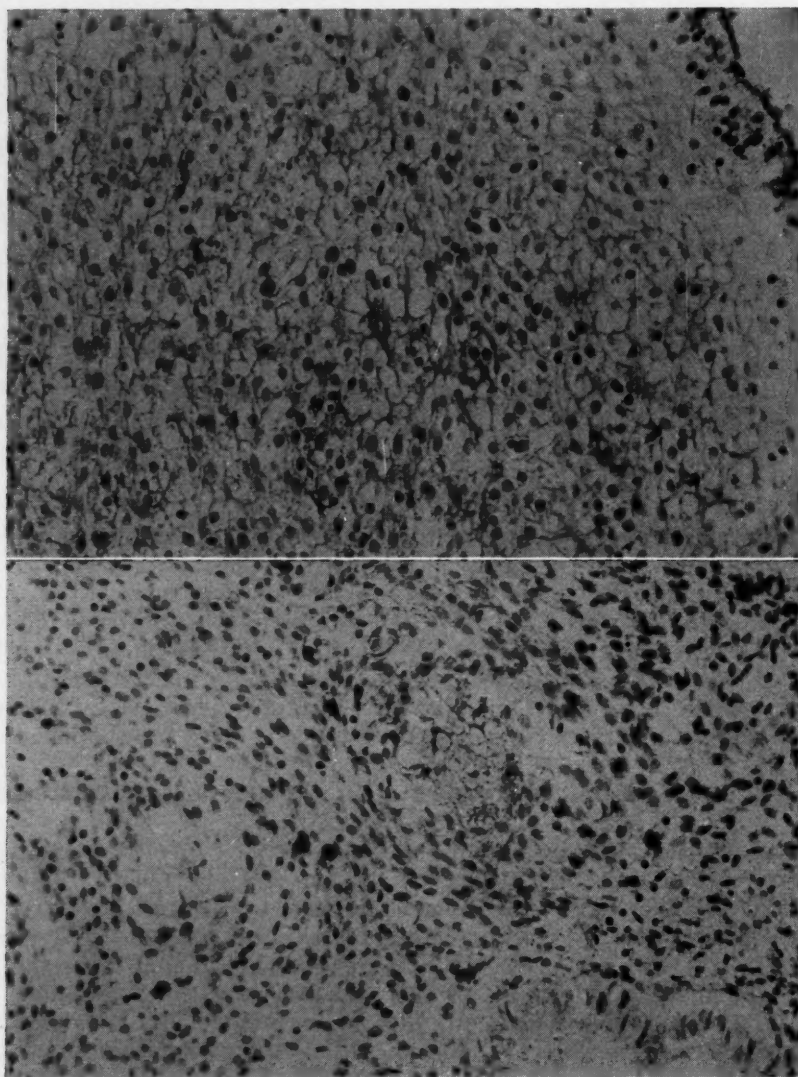
Fig. 2.

Fig. 1.—Proliferative endometrium. The metachromatic material is present in an interlacing network between stromal cells. (×180.)

Fig. 2.—Proliferative endometrium. Several mast cells are present in the stroma. (×180.)

and was never seen in the stroma of the basal layer except in the earliest stage immediately following menstruation. Metachromasia was not seen in the epithelial cells of the glands except for a faint reaction in the cytoplasm

in a few examples of mid-proliferative endometrium. Mast cells were present in all examples of proliferative endometrium (Fig. 2). These were present in moderate numbers and were scattered diffusely throughout the stroma. The metachromasia of the mast cell granules was much more intense than that of the stromal intercellular material. In a few instances the scant secretions in the gland lumina were faintly metachromatic.

Fig. 3.
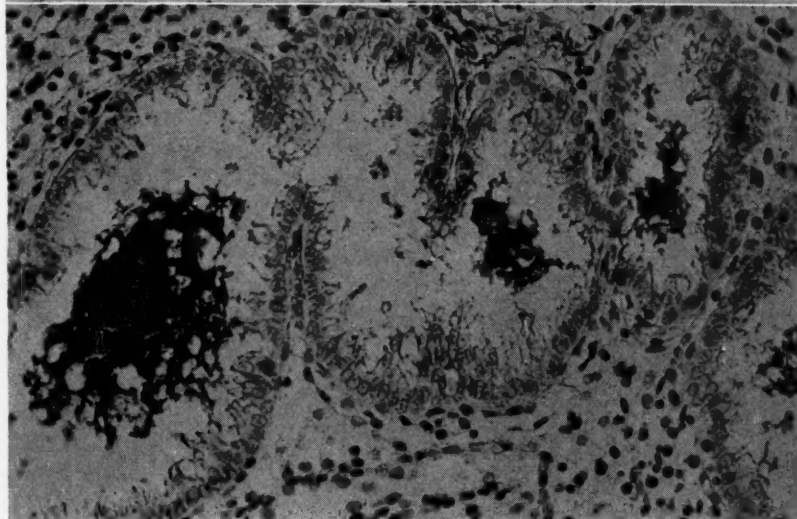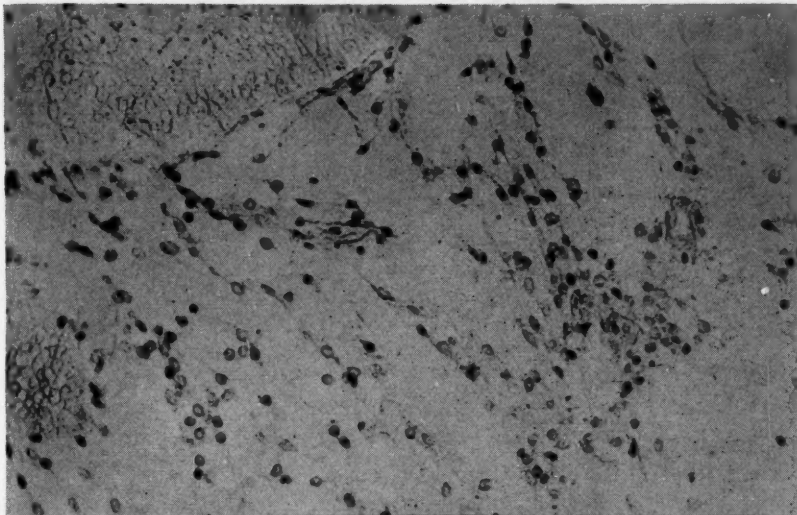
Fig. 4.

Fig. 3.—Twenty-day secretory endometrium. The stroma is edematous and there is no intercellular metachromasia. (×180.)

Fig. 4.—Twenty-day secretory endometrium. The secretion in the gland lumina is metachromatic in patches. Parts of the secretion take a dark blue rather than lavender stain. (×180.)

Early Secretory Endometrium (sixteen to twenty-two days).—The stromal metachromatic substance was not observed in early secretory endometrium (Fig. 3). None of the epithelial cells showed metachromatic staining. Nuclei were blue and the cytoplasm was either clear or blue. Mast cells in most

of these specimens were completely absent; one or two mast cells were seen in a few instances. The secretions in gland lumina throughout the secretory phase were prominently metachromatic (Fig. 4).

Late Secretory Endometrium (twenty-three to twenty-six days).—Intercellular stromal metachromasia was present in these specimens between the predecidual cells immediately beneath the surface epithelium and around blood

Fig. 5.
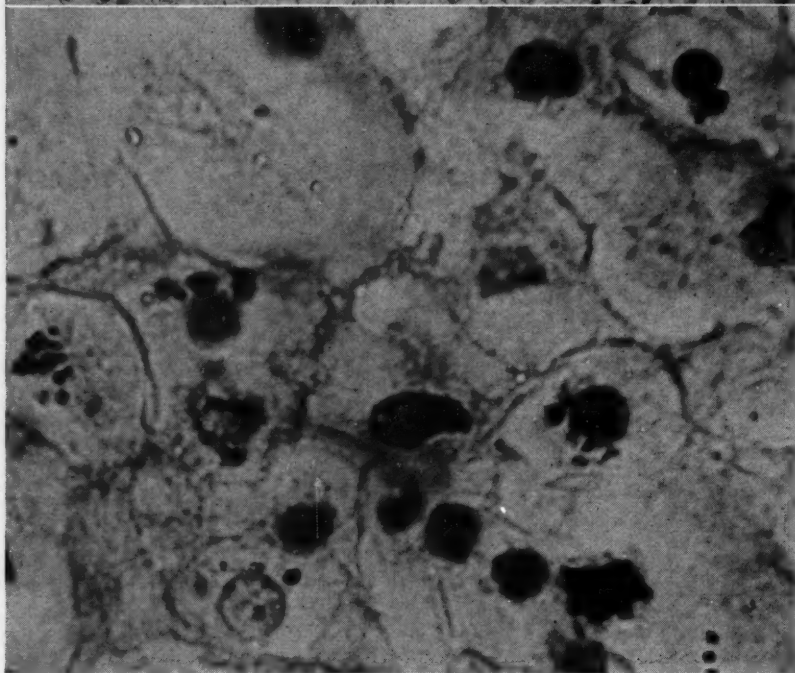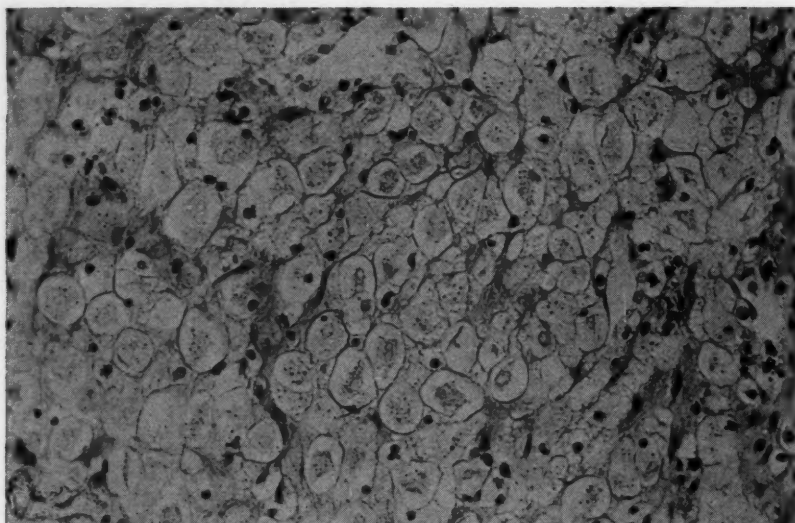
Fig. 6.

Fig. 5.—Early pregnancy. Metachromatic material is present between the early decidual cells sharply outlining the cells. (×180.)

Fig. 6.—Early pregnancy. Small and large metachromatic granules are present in the cytoplasm of the early decidual cells. (×1150.)

vessels. Mast cells were more numerous in these specimens than in those of early secretory endometrium. In addition, tiny irregular granules were seen in the cytoplasm of the predecidual cells. These were fewer in number than the granules in mast cells and were variable in size rather than uniform as in mast cells.

Fig. 7.
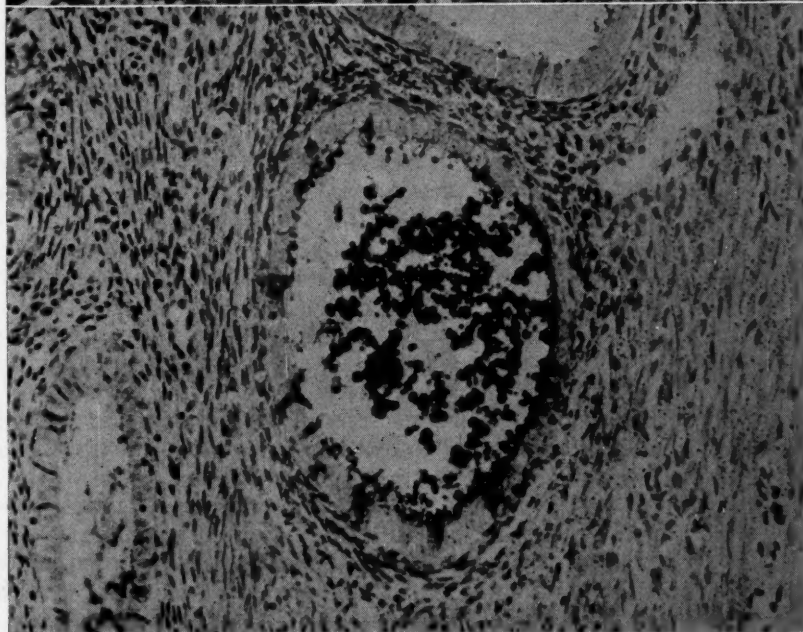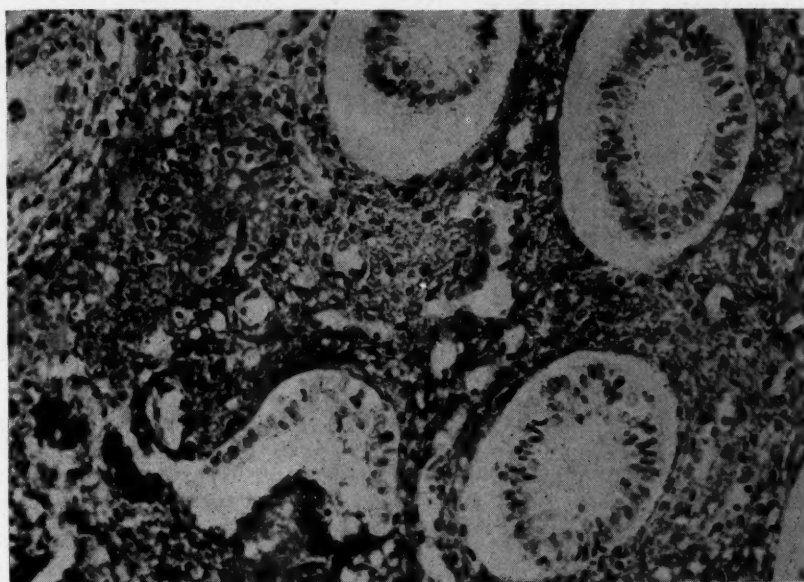
Fig. 8.

Fig. 7.—Cystic hyperplasia. There is a dense accumulation of metachromatic substance between the stromal cells. (×180.)

Fig. 8.—Cystic hyperplasia. One gland shows metachromatic secretions and a few of the epithelial cells contain a similar material. (×180.)

Endometrium of Early Pregnancy.—The metachromatic substances in this endometrium were similar in location to those of the late secretory phase but the stromal intercellular material stained more intensely (Fig. 5). Also the subintimal region of spiral arterioles gave an intense reaction, which was not noted in endometrial arterioles during the cycle. The intracytoplasmic granules which were present in predecidual cells were also seen in the early decidual cells (Fig. 6). The specimen of "secretory hyperplasia" was similar to the endometrium of pregnancy.

Myometrium.—Metachromasia in the myometrium was confined to the walls of arteries and to the numerous mast cells in the connective tissue immediately surrounding the vessels. There did not appear to be any change in the number of mast cells in this tissue during the menstrual cycle.

Cystic Hyperplasia.—These three endometria showed a marked increase in the intercellular stromal metachromasia. There were abundant accumulations around the dilated glands (Fig. 7). Mast cells were present in moderate numbers. One of the striking changes in this type was the appearance of intensely metachromatic material in the epithelial cells of some of the dilated glands (Fig. 8). It was present to a large extent in the basal portion of the epithelial cells next to the basement membrane. In a few cells it was present above the nucleus next to the lumen. The secretions in these gland lumina were strongly metachromatic.

Adenocarcinoma.—In neither of the cases of adenocarcinoma was there metachromatic substance in the epithelial cells of the tumor. These were rapidly growing tumors and contained many solid areas of epithelial cells. In the few strands of connective tissue traversing the tumors were a few scattered mast cells and a faint intercellular metachromasia.

Discussion

The finding of intercellular metachromatic substance in the endometrial stroma during the proliferative phase is in accord with the observations of Bensley,[4] Sylven,[5] and Wislocki and Dempsey.[9] The localization in the outer two-thirds is of some interest because it is in this area that the edema of the stroma occurs. We have not seen metachromasia in the basal one-third except in one case of a very early proliferative endometrium. In contrast to the upper two-thirds, the basal portion does not take part in the cyclic changes resulting in menstruation. Bensley[4] has noted that in the very earliest stage of proliferation there is a slight intercellular edema with no metachromasia. Metachromatic material appears shortly thereafter and is present in increasing amounts at the same time edema is absent during the proliferative phase. In the early secretory phase metachromasia disappears and edema reaches its peak. In the late stages of secretion, twenty-three to twenty-seven days, edema gradually disappears or diminishes and metachromasia reappears between the predecidual cells. It is present in the ground substance of the decidua compacta of the placenta (Wislocki and Dempsey[9]).

There appears to be a reciprocal relationship between the edema of the stroma of the endometrium and the intercellular metachromatic substance. Meyer[2] states that the acid mucopolysaccharide hyaluronic acid binds water in interstitial spaces. It may be that the intercellular substance in the endometrial stroma behaves in a similar way. The apparent disappearance of metachromasia during early secretion may mean that the mucopolysaccharide is depolymerized or disaggregated.

Incubation with hyaluronidase did not cause disappearance of the intercellular metachromasia although there resulted a slight diminution in the intensity of the stain. Therefore hyaluronic acid is probably not the major

acid mucopolysaccharide of the intercellular material. Wislocki and Dempsey[9] report that hyaluronidase affected none of the metachromasia encountered in the placenta and uterus except that of Wharton's jelly.

In late secretory endometrium, that beyond the twenty-third day, in some of the stromal cells surrounding blood vessels, namely predecidual cells, a few metachromatic granules of varying size were seen. Wislocki and Dempsey[9] have described similar cells in the decidua vera. These authors concluded that these are decidual cells and not macrophages. It was demonstrated that the metachromasia in the cytoplasm of these cells and of the large true decidual cells was abolished by ribonuclease and it was therefore concluded that this material was ribonucleoprotein. The granules in the predecidual cells of late secretory endometrium are probably ribonucleoprotein particles.

The increase in intercellular metachromasia in hyperplastic endometrium is quite striking. There also appears to be an increase in the number of mast cells. It should be noted that the number of mast cells in the endometrium is considerably less than the number in many other types of connective tissue (Janes and McDonald[10]).

The metachromasia of the cytoplasm of many epithelial cells in hyperplastic endometrium was much more intense than the faint reaction seen in normal proliferative endometrium. Most of the cells which contained it had clear cytoplasm when stained with phloxine-methylene blue. If this intra-epithelial substance were ribonucleoprotein, one would expect the cytoplasm to have a basophilic granular appearance when stained with phloxine-methylene blue. However, Atkinson and co-workers[11] have demonstrated basophilic particles in epithelial cells in hyperplastic endometrium and some of the metachromasia in these epithelial cells is probably due to ribonucleoprotein. The secretion of the glands in these hyperplastic endometria was metachromatic and many of the cells were bulging with the same material and appeared to be discharging it into the lumina of the glands.

In normal endometrium the scant secretion within the proliferative glands is faintly metachromatic whereas that of the secretory phase is strongly metachromatic. Atkinson and associates[11] have demonstrated that basophilic staining of the secretion of the proliferative phase is abolished by ribonuclease but that of the secretory phase is not. It seems likely that the secretions of the proliferative phase contain ribonucleoprotein, while the secretion of the secretory phase contains mucus in addition to ribonucleoprotein.

Summary

The changes in the metachromatic substance in the endometrium during the menstrual cycle have been described. Intercellular stromal metachromasia is present during the proliferative phase, diminished or absent during the early secretory phase, and reappears between the predecidual cells of the late stages of secretion. There appears to be a reciprocal relation between intercellular stromal metachromasia and edema of the stroma.

Mast cells are present during the proliferative phase, diminish in number or are absent in the early stages of secretion and reappear in moderate numbers in late secretion. They are present in slightly increased numbers in hyperplasia.

Metachromatic granules appear in predecidual cells in late secretory endometrium and these are probably ribonucleoprotein particles. Faint metachromasia was observed in the cytoplasm of epithelial cells in a few examples

of proliferative endometrium. Intense metachromasia was present in the cyto-
plasm of epithelial cells in hyperplastic endometrium. This probably repre-
sents ribonucleoprotein in part but some may be mucopolysaccharide. In-
cubation with hyaluronidase failed to abolish any metachromasia in the endo-
metrium.

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THE EFFECTIVENESS OF A HOSPITAL BIRTH CONTROL CLINIC

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STUDIES of the effectiveness of a birth control program have come largely from special centers. The importance of the hospital clinic has been generally recognized, but the experience of such intramural services has rarely been reported. For this reason a review of the work of a small clinic operating as a part of a university department of obstetrics and gynecology should be of some special interest.

A clinic to give contraceptive advice to its own patients was begun at the Sloane Hospital in 1925, two years after the opening of the first birth control clinic in America. From the beginning the service was limited to mothers discharged from the obstetrical wards after complicated pregnancies and to certain other women with serious chronic disease whose lives might be further endangered by additional pregnancies. Although during recent years there may have been some liberalization in interpretation there has been no departure from the original policy of giving advice only for specific health indications.

The Clinic Material

Since its inauguration twenty-four years ago, approximately 3,500 women have been seen in the clinic, representing less than 10 per cent of the total ward deliveries. The patients receiving this clinic service were all married, living with their husbands, and had had, almost without exception, at least one pregnancy.

The majority of the patients are now referred to the contraceptive clinic by the medical consultant to the obstetrical division after his review of the chart at the time of the patient's first follow-up visit, four to six weeks post partum. The services of the clinic have also been at the disposal of other departments of the Medical Center since 1937, but few patients have been referred with the partial exception of cases from the psychiatric division.

Indications

The indications for giving contraceptive advice are shown in Table I, which is based on a sample of 529 recent patients. The importance of toxemia of pregnancy is shown by the 181 patients who were advised against immediate conception for this reason. Other important indications are tuberculosis and cardiac disease, which with toxemia of pregnancy accounted for 56 per cent of the patients.

That there was an incomplete coverage of such patients by the contraceptive clinic is shown by a comparison of the frequency of these disorders on the ward and the number of patients reaching the clinic. Of the approximately 36,000 women delivered on the ward service since 1925, 18 per cent have had complica-

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tions of toxemia, cardiac disease, or tuberculosis. But of the total women delivered, only 9.7 per cent were seen in the clinic for all reasons.

Since the clinic has been strictly limited to the patients presenting a medical contraindication to pregnancy, this group of patients has had a special motivation for the avoidance of pregnancy. The study of the effectiveness of the work of the clinic assumes a special significance when this point is borne in mind.

TABLE I. INDICATIONS FOR CONTRACEPTIVE INSTRUCTION

Previous toxemia of pregnancy	181	
Cardiac disease	83	56.3%
Tuberculosis	34	
Convalescent surgical patients	40	
Severe secondary anemia	33	
Psychiatric disorder	47	
Previous cesarean section	20	
Multiparity	15	
Thrombophlebitis	9	43.7%
Pyelitis	9	
Diabetes	7	
Neurologic indications	12	
Miscellaneous medical conditions	39	
Total	529	

Method of Contraception Advised

The contraceptive method of choice recommended by the clinic has been the diaphragm-jelly technique. Other occlusive techniques such as the cervical cap and the Messinga diaphragm were occasionally used in patients with anatomical defects. These were given up some time ago on account of apparent unreliability so that now the only alternative method prescribed is the rubber sheath and jelly. The routine of the clinic has been organized on simple lines. New patients are instructed in the use of the diaphragm in small groups with the aid of the usual anatomical models. Each is then individually instructed and discharged only after she has inserted the diaphragm properly. For this report only the patients fitted with the diaphragm were used.

Statistical Methods

For the purpose of determining the effectiveness of the advice given on the subsequent fertility of these 3,500 patients, a random sampling of 500 patients was considered to be sufficient from a statistical standpoint. A total of 529 patients was actually used. These were selected from those attending the clinic between the years 1931 and 1940, inclusive, which permitted fairly long periods of subsequent observation.

The postclinic fertility of each patient was recorded from the hospital chart up to the closing of the record, this constituting a somewhat variable period of observation. The collection of the data in this manner did not permit the evaluation of certain aspects of effectiveness, such as acceptability, how long the method was used, and when discontinued.

It has been standard practice in analyzing the effectiveness of the work of birth control clinics statistically to measure the chance of conception by adopting a unit of measure to the risk of pregnancy. The unit employed is the "woman-month." For a matter of convenience, the measure is usually stated in the form of pregnancy rates per hundred "woman years" of exposure to the chance of pregnancy. For the purpose of computing the rates, the duration of exposure is determined by subtracting from the total elapsed time of married life, those months as in pregnancy and lactation in which it was physiologically impossible

to become pregnant. The pregnancy rate per one hundred years of exposure is then calculated by the formula:

$$P_R = \frac{\text{Total number of pregnancies}}{\text{Total months of exposure}} \times 1200$$

In order to determine the true effectiveness of a birth control clinic it is necessary to compare the postclinic pregnancy rates with normal rates to be expected without such advice. This is usually taken from the preclinic pregnancy rate for the same group although this permits certain errors.

Statistical studies of uncontrolled pregnancy rates all show a high chance of first conception.[4] After the first pregnancy, however, there is a steady decline in fertility with advancing age and duration of marriage. This decline in the chance of conception for all pregnancies after the first one depends to a large extent on postpartum lactation and amenorrhea. To these, such factors as frequency of coitus, and pelvic disease probably add their weight. These factors are probably responsible for the small differences in the uncontrolled rates reported from the several geographically scattered clinics.

Previous reports on the preclinic pregnancy rate are shown in Table II. These demonstrate the variability in different areas of uncontrolled pregnancy rates when no contraception has been used. They also show the relative effectiveness of contraceptive methods employed even before formal clinic instruction in reducing fertility.

TABLE II. EFFECT OF PRECLINIC CONTRACEPTIVE EFFORTS ON PREGNANCY RATES IN VARIOUS CLINICS

INVESTIGATION	COLOR	WITHOUT CONTRACEPTION	WITH CONTRACEPTION
New York City[2]	White	105	27
Cincinnati[2]	White	93	55
Logan County[4]	Negro	88	56
Logan County	White	84	45
Spartanburg, S. C.[2]	Negro	82	58
Spartanburg	White	71	43
Rural Kentucky[6]	White	70	26
Watauga County[7]	White	64	13
Sloane Hospital Clinic*		74	29

*Conceptions per 100 women years of exposure to the risk of pregnancy:

$$P_R = 1,200 \times \frac{\text{Conceptions}}{\text{Months of Exposure}}$$

The hospital records available for this study did not include data on the preclinic contraceptive practices of this group of patients. Their uncontrolled pregnancy rates could not therefore be directly determined. The figures used for the Sloane Hospital clinic appearing in Table II were obtained from a small series of patients subsequently seen in the clinic but not those of the group under analysis. The uncontrolled pregnancy rate for this especially questioned group was found to be 74. With this observed figure and with the background of the other figures in Table II, an uncontrolled pregnancy rate of 80 per hundred years of exposure was chosen to compare against the postclinic rates in the Sloane Hospital clinic.

Comparison of the results must also be made with those of the extramural clinics which are shown in Table III. Their experience with the more simple techniques, such as jelly alone, foam powder, and sponge used mostly in the rural areas, indicates that these methods are relatively subject to failure. All of the statistical studies, however, on the use of the occlusive diaphragm and jelly have established that this technique provides a high degree of protection. The pregnancy rates reported, ranging from 6 to 13 hundred years of exposure, indicate an effectiveness of 85 to 94 per cent.

TABLE III.   RELATIVE EFFECTIVENESS OF VARIOUS CONTRACEPTIVE TECHNIQUES

METHOD AND RESIDENCE	YEARS OF EXPOSURE	PREGNANCIES	
		NUMBER	RATE
Diaphragm and jelly:			
Philadelphia[9]	935	59	6
Port Chester, N. Y.[10]	472	32	7
New York City[4]	703	65	9
Cincinnati[4]	2,703	244	9
Nashville[11]	361	32	9
Spartanburg, S. C.[4]	671	87	13
Sloane Hospital Clinic	2,348	312	13*
Condom:			
Watauga County[7]	604	68	11
Foam powder and sponge:			
Nashville[11]	206	57	28
New York City[12]	82	29	35
Jelly alone:			
Philadelphia[13]	60	9	15
Chicago[14]	241	47	20
Rural Kentucky[6]	204	41	20
Logan County[4]	938	354	38

*Of 34 pregnancies reported by patients responding to the questionnaire sent out, 23 were listed as planned, and 11 as unplanned, or 11 accidental pregnancies in 194 years of exposure which corresponds to a rate of 6 per hundred years of exposure.

Results of the Work of the Sloane Clinic

The 529 women in this series were under observation for a total of 2,558 years during which time they reported 312 conceptions, giving an aggregate exposure to the risk of pregnancy of 2,348 years.   The 312 conceptions result in a pregnancy rate of 13 per hundred years of exposure which against the background of an uncontrolled rate of 80 per hundred years gives an effectiveness of 84 per cent.

TABLE IV.   INCIDENCE OF PREGNANCY IN SUCCESSIVE YEARS AFTER CLINIC INSTRUCTION

YEARS UNDER OBSERVATION	NUMBER OF PATIENTS	YEARS OF EXPOSURE	NUMBER OF PREGNANCIES	PREGNANCY RATE
0 and 1	89	64	28	44
2	71	125	29	23
3	58	152	33	22
4	52	189	29	15
5-7	150	814	104	13
8-10	77	634	65	10
11 and over	32	370	24	6
Total	529	2348	312	13

Many of the patients, however, were referred to the clinic because of conditions transitory in nature which did not require permanent avoidance of pregnancy.   Others suffered from a relatively mild chronic disorder which allowed for further pregnancies after a period of rest.   To explore this point a questionnaire was sent to all patients reporting pregnancies.   The information obtained was very incomplete, although those who replied reported a high incidence of planned pregnancies.

The small group answering the questionnaire yielded an aggregate of 206 years of exposure from the first clinic attendance to discontinuance of contraception, with 34 pregnancies corresponding to a rate of 16 per hundred years of exposure.   This is not much different from the rate of 13 found in the larger series.   Of the 34 pregnancies, 23 were listed as planned and 11 as unplanned.

Thus the accidental pregnancies were 11 in 194 years of exposure which corresponds to a rate of 6 per hundred years of exposure, and an effectiveness of 92 per cent.

The pregnancy rates when tabulated by years under observation, Table IV, show many accidental pregnancies the first year after enlistment. This observation is similar to that made by Stix who found this high incidence of failure in the first year in all three areas which she reported.[3]

The outcome of the 312 reported pregnancies is presented in Table V by years under observation. The point of chief interest for this study is the large number of accidental pregnancies occurring during the first and second years that required termination by therapeutic abortion. Of 57 such pregnancies, 26 required termination, and 24 patients were sterilized at the time of interruption of the pregnancy. Out of the entire 312, there were 61 therapeutic abortions, or one in five, which may be taken as an indication of the relative severity of the indications for which the original advice was given.

TABLE V. OUTCOME OF PREGNANCIES OCCURRING IN VARIOUS YEARS AFTER BIRTH CONTROL INSTRUCTION

YEARS UNDER OBSER- VATION	NUMBER OF PATIENTS	AGGREGATE YEARS OF OBSER- VATION	AGGRE- GATE YEARS OF EX- POSURE	TOTAL PREG- NANCIES	VIABLE BIRTHS	THERA- PEUTIC ABORTIONS	OTHER* ABOR- TIONS
0	20	11 ⎫	64	28	13	14	1
1	69	69 ⎭					
2	71	142	125	29	14	12	3
3	58	174	152	33	22	7	4
4	52	208	189	29	19	3	7
5	55	275	250	37	26	6	5
6	53	318	299	26	21	3	2
7	42	294	265	41	30	5	6
8	31	248	233	34	28	3	3
9	27	243	227	22	17	3	2
10	19	190	184	9	7	1	1
11	10	110	103	10	7	2	1
12	14	168	163	8	4	2	2
13	7	91	88	4	4	–	–
17	1	17	16	1	1	–	–
Total	529	2558	2348	312	213	61	38

*These include both spontaneous and induced abortions.

The chance of failure bore no significant relation to age until the year 35 was reached (Table VI). After this it declined sharply and the risk after 40 years was only about half of the general average.

TABLE VI. RELATION OF PREGNANCY RATES TO PATIENTS' AGE AT TIME OF RECEIVING CONTRACEPTIVE ADVICE

AGE OF PATIENT (YEARS)	YEARS OF EXPOSURE	NUMBER OF PREGNANCIES	PREGNANCY RATE
16-24	255	39	15
25-29	516	96	19
30-34	660	91	14
35-39	582	64	11
40 and over	335	22	7
Total	2348	312	13

Comment

In the light of the experience of the extramural clinics, it is interesting to speculate how such a degree of effectiveness was actually obtained by the patients of this report. It is the general opinion that about half of the women in any clinic series abandon the prescribed method within a period of two years. Yet it is believed that the influence of the clinic advice remains by increasing the care and effectiveness with which subsequent methods are used.

The fairly long periods of observation afforded by the Sloane Hospital data suggests a combination of factors. Any fairly conscientious contraceptive effort, no matter what the method, aided by the natural decline in fertility, would probably be enough to reduce fertility to the degree of effectiveness reported here. The slope of this decline may be steeper for a population of average fertility and special motivation for avoiding pregnancy, as represented by the Sloane series, as compared with the perhaps more fertile group from birth control clinics.

A disturbing factor in this study was the large number of therapeutic abortions necessary. The pattern of contraceptive failure the first few months which seems to run through most of the studies regardless of method suggests that this high risk can only be avoided by more sterilizations. Possibly a more diversified and controlled contraceptive program would also have avoided some of these accidental pregnancies.

Summary and Conclusions

A series of 529 patients selected at random from 3,500 women attending a hospital birth control clinic was reviewed to determine the clinic's effectiveness. These patients were under observation for a total of 2,558 years during which time they reported 312 conceptions giving an aggregate exposure to the risk of pregnancy of 2,348 years. This corresponds to a rate of 13, indicating an effectiveness of 84 per cent. A smaller group of patients in which additional data permitted the subtraction of planned pregnancies gave corrected figures indicating an effectiveness of 92 per cent. This degree of effectiveness compares favorably with that of the special extramural birth control clinics.

The failures which have been brought out by the data suggest the possibility of certain improvements. To avoid the risk of too many accidental pregnancies for the immediate period following instruction, management should be more diversified and selective. The more simple methods might be supplemented by determination of ovulatory time by basal body temperatures. Sterilization should be resorted to more frequently where the risk to pregnancy is particularly serious.

Finally, more concentrated effort should be made to reach every patient with the proper indications. This effort should be concerned not only with postpartum women but with all patients under care in any department of the hospital for conditions which give a significantly increased hazard to pregnancy.

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"PELVIC DRIVE" IN OBSTETRICS: AN X-RAY STUDY OF 100 CASES*

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STEREOROENTGENOGRAPHIC studies of the pelvis during pregnancy and labor by Caldwell, Moloy, and D'Esopo, resulted in the establishment of a morphologic classification of pelvic type[1] and a revision of our concepts of engagement and the mechanism of labor.[2]

While studying the mechanism of labor, Caldwell and his associates pointed out that the soft parts play a role in directing variations in the position of the curved axis of fetal descent within the bony pelvis. The three axes of descent they demonstrated are descent in the axis of the posterior, mid-, or forepelvis. They postulated that it is not chance alone that causes the fetus to descend through one of these axes, but rather that certain supporting structures of the lower uterine segment and cervix help to determine the pelvic axis of fetal descent in each case.[3] The rationale in this regard is that the position of the lower uterine segment and cervix are determined by the fascial supports of the uterus, and that the physical state of the fascial attachments and their reaction to the forces of labor may cause a change in the position of the cervix and thus direct the fetal presenting part into the posterior, mid-, or forepelvis.

This concept implies prognostic import. Its further study may give a clue to the better handling of cases of abnormal and inefficient labor.

Several years ago, Dr. Caldwell suggested to me that perhaps an indirect study of the axis of fetal descent within the pelvis (without actually visualizing the pelvic soft parts by use of contrast media) might be made by studying the position of the fetal back in relation to the maternal vertebral column during or just before onset of labor, by pelvimetric methods.

From a purely mechanical viewpoint, alterations in the position of the fetal back alter the position of the fetal presenting part along the direction of an arc, so that when the fetal back is posterior the presenting part is anterior and conversely.

In Figs. 1, 2, and 3, which are photographic reproductions of lateral roentgen views showing fetopelvic relationship, it is evident that the fetal presenting part maintains a constant relationship to the fetal back. In Fig. 1, where the fetal back is anterior in relation to the maternal spine, the presenting part is being directed into the posterior pelvic segment of the inlet. In Fig. 2, where the fetal spine lies midway between the symphysis in front and the maternal spine posteriorly, the presenting part is being directed through the middle of

the inlet, and in Fig. 3, the fetal back being in close relation to and parallel to the maternal spine, the presenting part is being directed into the forepelvis and against the symphysis.

After viewing a large number of lateral films, it was seen that the fetopelvic relationship definitely fell into one of the three categories previously mentioned. It was also noted that one can visualize the formation of an angle between the fetal and maternal spines. It was decided to coin a term and call this angle the "drive-angle." Where the "drive-angle" approaches 90 degrees, the drive is into the posterior pelvis. Where the "drive-angle" is more acute than 90 degrees, the drive is into the middle of the pelvis, and in its most acute phase, where the "drive-angle" tends to parallel the maternal spine, the drive is into the forepelvis.
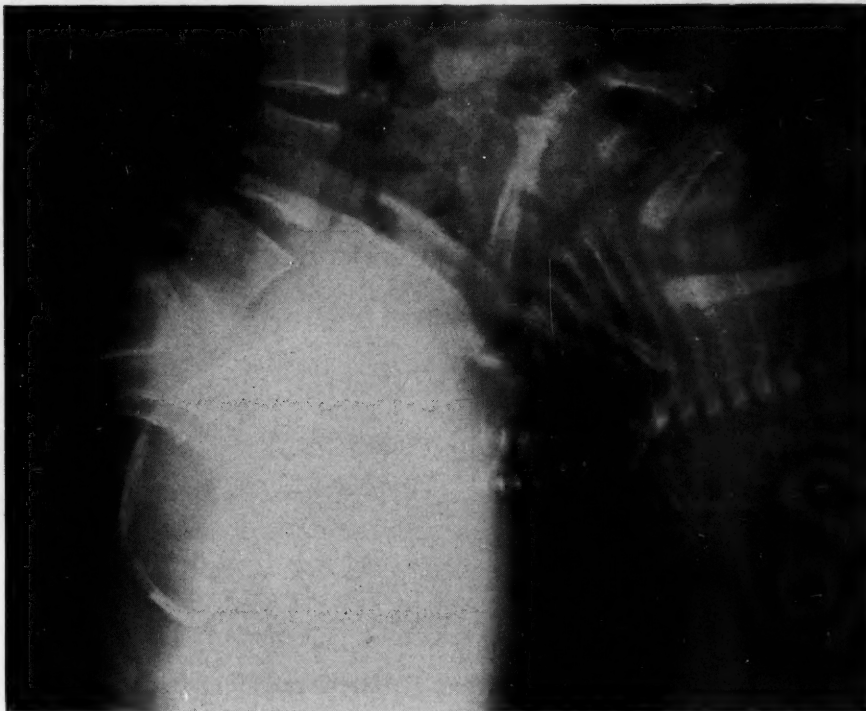
Fig. 1.—Demonstrating posterior pelvic drive.

Since every case x-rayed by the Caldwell-Moloy technique could be placed into one of these three groups it was thought that an interesting study could be made of the relationship of drive and "drive-angle" to labor. This paper therefore is a presentation of the data accumulated in this study.

One hundred cases x-rayed at the Jewish Hospital of Brooklyn during the years 1945, 1946, and 1947 were used. Each case was used in which the "drive-angle" was clearly discernible on the lateral film. Occasionally plates were seen which failed to show adequately the fetal and maternal spines; these were therefore not included in the series. Similarly, no cases showing breech presentation were used.

It must be stated here that routine x-ray pelvimetry is not practiced in the Department of Obstetrics at this hospital. Only suspected dystocia cases are so x-rayed. Thus each case in this series presented a potential or actual problem to the staff. Both ward and private cases are included in the study.

Fig. 2.—Demonstrating midpelvic drive.

All 100 cases were broken down into three groups for clarity and ease in comparison:

Group I: Posterior pelvic drive. "Drive-angle" 90 degrees (approximate).

Group II: Midpelvic drive. "Drive-angle" 45 degrees (approximate).

Group III: Forepelvic drive. "Drive-angle" less than 45 degrees. Roughly where the fetal vertebral column parallelled the maternal vertebral column.

TABLE I. INCIDENCE

Group I	48 cases	48%
Group II	34 cases	34%
Group III	18 cases	18%

TABLE II. PARITY SERIES

The 100 cases in the series were distributed with regard to parity as follows:

Primiparas	84 cases	84%
Multiparas	16 cases	16%

TABLE III. PARITY GROUP

The percentage of multiparity in each group is as follow:	
Group I	18.6%
Group II	11.7%
Group III	16.6%

The incidence of multiparity being stable between the groups we feel eliminates the possibility that the lax abdominal musculature of the multipara allows the fetal back to come far anterior thus giving a "drive-angle" of 90 degrees and so contributing to a posterior pelvic drive.
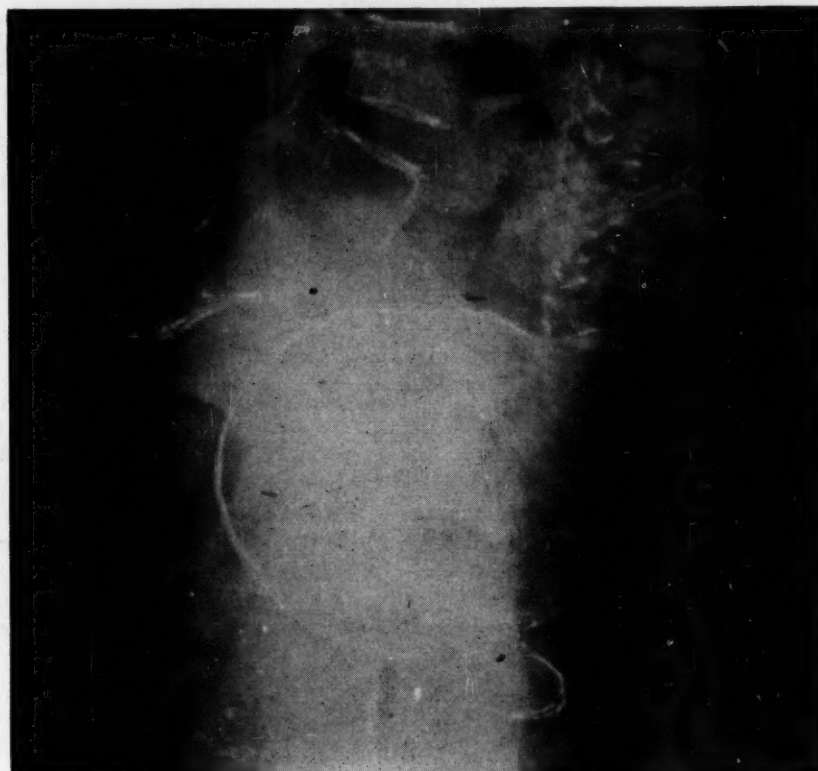
Fig. 3.—Demonstrating forepelvic drive.

TABLE IV. RELATIONS OF DRIVE AND "DRIVE-ANGLE" TO PELVIC TYPE

	GROUP I (POSTPELVIC)	GROUP II (MIDPELVIC)	GROUP III (FOREPELVIC)
Gynecoid	(33) 68.7%	(14) 41.1%	(3) 16.6%
Android	(7) 14.6%	(11) 32.3%	(11) 61.1%
Anthropoid	(6) 12.5%	(7) 20.5%	(2) 11.1%
Platypelloid	(2) 4.1%	(2) 6.0%	(2) 11.1%

In these figures can be seen a consistent and definite trend. As we go from the advantageous posterior pelvic drive to the abnormal forepelvic drive we observe: (a) a progressive diminution in the percentage of the gynecoid pelvis, (b) a progressive increase in the percentage of the android pelvis, (c) a progressive increase in the percentage of the platypelloid pelvis, (d) a constancy in the percentage of the anthropoid pelvis.

The incidence of the platypelloid pelvis is at a much higher level than in Caldwell's reports on its incidence in skeletal material (2.6 per cent) or in his report on 215 primigravid women (0.9 per cent). This can be explained on the basis that this series is one where each case was suspected of dystocia and was x-rayed for that reason.

TABLE V. RELATION OF DRIVE AND "DRIVE-ANGLE" TO DURATION OF LABOR

Group I (postpelvic)	17.8 hours
Group II (midpelvic)	25.2 hours
Group III (forepelvic)	17.4 hours

These are the averages of total duration of labor of 39, 23, and 12 patients, respectively in Groups I to III. There were 25 patients delivered by cesarean section who were not included, for it was not deemed advisable to average the time of trial labor in duration of labor statistics.

It is of interest to note an approximately 50 per cent shorter duration of labor in Group I as compared with Group II cases. We also wish to point out that in Group III there were six cesarean sections (33.3 per cent of the group). These cases were not averaged into the duration of labor statistics, thus accounting perhaps for the failure of a progressive increase in duration of labor from Group I to Group III.

TABLE VI. RELATION OF DRIVE AND "DRIVE-ANGLE" TO TYPE OF DELIVERY

TYPE OF DELIVERY	GROUP I (POSTPELVIC)	GROUP II (MIDPELVIC)	GROUP III (FOREPELVIC)
Spontaneous	(13) 27.0%	(12) 35.3%	(3) 16.6%
Low forceps	(21) 43.7%	(4) 11.8%	(6) 33.3%
Combined low forceps and spontaneous	70.7%	47.1%	49.9%
Midforceps	(4) 8.4%	(7) 20.6%	(3) 16.6%
Cesarean section	(8) 16.6%	(11) 32.3%	(6) 33.3%
Miscellaneous*	(2) 4.2%	-----	-----

*One version; multipara, vertex floating at full dilatation; 26 hours' labor. One craniotomy; hydrocephalic; 50 hours' labor.

In these figures too can be seen a consistent and definite trend. As we go from the advantageous posterior pelvic drive to the abnormal forepelvic drive we observe: (a) a diminution in spontaneous and low forceps delivery, (b) an increase in percentage of midforceps delivery, (c) a 100 per cent increase in percentage of cesarean section.

While even the incidence of section in Group I is surprisingly high (cesarean section incidence at this hospital averaging 4.5 per cent), it was pointed out at the beginning of this paper that all these patients were dystocia suspects and for this reason x-ray pelvimetry was done. Thus a very definite correlation exists between drive and "drive-angle" and type of delivery. The correlation is a positive one, namely, the association of advantageous drive with the greatest incidence of normal delivery and the association of abnormal drive with the greatest incidence of operative delivery, whether from below or through the abdomen.

The above analysis was so positive it was thought that perhaps pelvic size might have something to do with the statistical results. Since we were interested in studying drive and "drive-angle" alone and wished to eliminate extraneous factors where possible, we measured the anteroposterior diameter of the inlet wherever possible in cases in each group.

Of the 100 cases studied in this series, anteroposterior diameter of inlet measurements are available in 91 cases, the group averages of which are seen

in Table VII. The figures show that the anteroposterior diameter of inlet measurements in the cases of each group are almost identical so that this factor could not have modified the results obtained so far as type of delivery was concerned.

TABLE VII. ANTEROPOSTERIOR DIAMETER OF INLET MEASUREMENTS

Group I (46 cases)	11.3 cm.
Group II (29 cases)	11.4 cm.
Group III (16 cases)	11.0 cm.

Discussion

This study has shown that three positions of the fetal back in relation to the maternal vertebral column on x-ray pelvimetry are associated with three directions of pelvic drive and three different "drive-angles." This fact gives indirect yet easily observed confirmatory evidence of Caldwell, Moloy, and D'Esopo's original hypothesis that the fascial attachments of the lower uterine segment and the cervix direct the presenting part into the fore, mid-, or posterior pelvis. Our study discloses, in addition, that pelvic morphology too plays a role in this regard, since our figures show a rise in the incidence of android and platypelloid pelves as the fetal back is displaced posteriorly and the pelvic drive becomes forepelvic and the "drive-angle" becomes more acute and tends to parallel the maternal spine. Uterine force is apparently dependent on this factor as the duration of labor increases as the drive and "drive-angle" become more abnormal. We have ruled out the possibility of multiparity with its attendant laxity of abdominal musculature contributing to pelvic-drive variations.

We feel further that an evaluation of drive and "drive-angle" should be incorporated in the interpretation of x-ray pelvimetry as these two factors are of prognostic import as the above results have shown: namely, increase in duration of labor, decrease in incidence of spontaneous and low forceps delivery, and increase in incidence of midforceps and cesarean section as we go from posterior-pelvic to forepelvic drive and their respective "drive-angles."

The results of this study suggest a practical application. In cases of slow or arrested progress in labor, it is ralatively common practice to utilize a tight abdominal binder. Several cases have been x-rayed at the Sloane Hospital for Women, before and after the application of such binders on a patient in labor. These plates have shown that with the binder, the fetal back is displaced backward toward the maternal vertebral column so that the "drive-angle" becomes acute or even parallels the maternal spine so that the pelvic drive becomes forepelvic.[4] In the light of our results in the current study on drive and "drive-angle" we can conjecture how detrimental to labor such practice becomes. It would appear to be much better practice to have such patients labor out of bed, walking or on their feet, so as to throw the weight of the pregnant uterus forward mechanically and thus achieve a good "drive-angle" with posterior pelvic drive.

Summary and Conclusions

1. The phrase "drive-angle" has been coined and explained.

2. A study of the relationship of drive and "drive-angle" to labor has been presented.

3. A positive correlation has been shown to exist between drive and "drive-angle," and pelvic type, duration of labor, and type of delivery.

4. Drive and "drive-angle" have been offered as additional points to be evaluated in the interpretation of x-rays taken before and during labor, since they have prognostic import.

5. It is suggested by this study that the use of the obstetric binder may be harmful to the progress of labor.

6. The thought is advanced that perhaps advantageous drive and "drive-angle" may be more frequently achieved by the simple expedient of permitting the parturient to remain on her feet as long as is possible and feasible during the first stage of labor.

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ABNORMAL BLEEDING IN OBSTETRICAL AND GYNECOLOGICAL CONDITIONS*

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RECENT reports by Allen and co-workers[1] show that in many conditions complicated by hemorrhage, there is an abnormality which may be detected by titration of heparinized blood with protamine.[2] This is a report of an investigation on patients who exhibit bleeding or bleeding tendencies associated with various obstetrical and gynecological conditions, including normal pregnancy and delivery. The method of study includes determination of: (1) the protamine titration, (2) whole blood clotting time, (3) thrombocyte counts, (4) prothrombin activity, and (5) gross observation of clot retraction and fibrinolysis. In some of the cases where active spontaneous bleeding was present and an increased protamine titration was demonstrated, treatment with the antiheparins toluidine blue and/or protamine sulfate was instituted.

Clinical Observations

Normal Pregnancy and Delivery.—
Twenty-eight normal pregnant women, chosen at random from clinic patients, were studied the day before delivery and again at irregular intervals throughout the postpartum period. Sixteen of these women were found to have increased protamine titrations before delivery, thirteen of this group returned to normal titrations before the tenth postpartum day. Twelve patients had normal protamine titrations predelivery; however, eight of these showed increased titrations at some time during this period, most of whom returned to normal before discharge. We found no consistent change in the clotting time or prothrombin activity, but there was an increase in the thrombocyte counts in these patients from predelivery throughout their postpartum period. No abnormal bleeding or morbidity was noted in any of these patients regardless of the value of their protamine titrations.

Hypermenorrhea.—
Thirty-one patients reporting hypermenorrhea were studied. Of nineteen patients observed during the menstrual period, usually on the second day of flow, fourteen had an increased protamine titration. Of the nineteen patients examined between menses, nine had increased protamine titrations. Elghammer and associates[3] have shown that in twenty-three women with normal menstrual periods used as controls, five had increased protamine titrations during menses and of thirty-five titrations made on these women between menses, eleven were increased.

Nine patients were given 50 mg. of protamine sulfate (Lilly) intramuscularly during the menstrual period and 100 mg. capsules of toluidine blue (Abbott) orally twice daily after meals for three to four days. Six of the patients treated had increased protamine titrations and all reported good results from therapy. Of the three patients whose titrations were normal, one reported good results, one reported fair results, and one reported no effect from therapy. Good results were interpreted as a return to normal flow and duration of menstruation. A few of the patients receiving oral toluidine blue capsules reported slight nausea even though the capsules were taken after meals. One patient reported severe nausea, and one reported burning on urination after taking toluidine blue capsules. The blue color of the urine was of no consequence but the patient was always informed of this phenomenon.

Four patients having hysterectomies for hypermenorrhea and polymenorrhea were studied prior to and following surgery. All had increased titrations preoperatively and all returned to normal two to three days following surgery without any specific therapy.

Postpartum Hemorrhage and Postoperative Bleeding.—

Four patients having postpartum hemorrhage, and six with postoperative bleeding were studied. All of these patients had increased protamine titrations at the time of bleeding and were treated with toluidine blue intravenously, 300 mg. in 500 ml. of normal saline, and/or protamine sulfate 50 mg. intramuscularly given every six hours. In each case bleeding stopped without the necessity of surgical intervention. Some of the patients receiving toluidine blue were nauseated during the period of injection. In one case toluidine blue infiltrated the tissues at the point of injection and although there was no slough, the area was very tender and superficial cellulitis persisted for many days.

Case Reports

CASE 1.—E. M., aged 28 years, No. 452813, had a normal delivery on March 13, 1949, with no excessive bleeding. On March 17, 1949, she had vaginal bleeding with many clots. The protamine titration was increased and 50 mg. of protamine sulfate were given intramuscularly and repeated every six hours until March 19, 1949. Bleeding had stopped on March 18, 1949, and the titration was normal the following day. No blood transfusions were given.

CASE 2.—A. S., aged 25 years, No. 371292, had vaginal bleeding nine days following normal delivery. A dilatation and curettage were performed and a very small amount of decidual tissue was removed. Bleeding continued and on the following day the protamine titration was found to be increased. She was given protamine sulfate 50 mg. intramuscularly every six hours until the titration was normal three days later. Bleeding stopped after the third injection.

CASE 3.—I. G., aged 23 years, No. 388507, had a normal delivery eleven weeks prior to study. She had slight vaginal bleeding at the time she left the hospital, which increased in amount so that five weeks post partum vaginal bleeding was heavier than a normal menstrual flow. Ergotrate was given which stopped the flow for one week. Vaginal bleeding again started, requiring five pads a day for one week. Again Ergotrate was given which stopped the bleeding for three days after which it recurred. A dilatation and curettage were performed seven weeks post partum, and no placental tissue was found. Bleeding continued until these studies were made, at which time the protamine titration was elevated to 0.18 mg. and the clotting time was prolonged to 47 minutes. Protamine sulfate, 50 mg. intramuscularly, was given every six hours and continued for four days. Bleeding had decreased on the second day and had stopped on the third day of therapy and did not recur; protamine titration was 0.16 mg. and clotting time was 31 minutes at this time.

Four weeks later she had a normal menstrual period at which time the protamine titration also was normal, 0.14 mg., and the clotting time was 35 minutes (normal clotting time 20 to 30 minutes).

CASE 4.—H. G., aged 23 years, No. 457423, had a vaginal hemorrhage twenty-four days post partum. She had a previous history of bleeding after tonsillectomy. The protamine titration was increased, and intramuscular protamine sulfate was started. Bleeding had stopped on the following day, and three days later the protamine titration was normal, at which time protamine sulfate was discontinued. No blood transfusion was given.

CASE 5.—J. M., aged 24 years, No. 466594, following normal delivery had a hematoma at the site of episiotomy which was evacuated but continued to ooze. The protamine titration was increased and protamine sulfate was started intramuscularly. Bleeding stopped after the first injection and protamine was discontinued on the second day of therapy at which time the titration was normal. No transfusions were given.

CASE 6.—J. J., aged 59 years, No. 389058, had a complete hysterectomy on Dec. 28, 1948. There was slight vaginal bleeding postoperatively and profuse vaginal bleeding occurred on Jan. 7, 1949. The protamine titration was elevated, and the patient was given toluidine blue intravenously on two successive days along with intramuscular protamine sulfate every six hours until Jan. 10, 1949. Bleeding was reduced to spotting on the second day of therapy and was entirely stopped on the fourth day of therapy. Whole blood, 500 ml., was given on the first day of therapy.

CASE 7.—D. H., aged 34 years, No. 138877, had a cervical biopsy taken on Feb. 3, 1949, which required hymenotomy. The patient had a severe vaginal hemorrhage on Feb. 9, 1949. Examination showed bleeding from both the cervical biopsy site and from the fourchette. At this time the protamine titration was elevated. Intramuscular protamine sulfate was given every six hours for four days. Bleeding had stopped on the second day of therapy, and the protamine titration was normal on the fourth day. Bleeding did not recur. No blood transfusion was given.

CASE 8.—R. V. H., aged 24 years, No. 437515, had a cesarean section for placenta previa on March 10, 1949. Bleeding was excessive at operation. The protamine titration was increased and toluidine blue, 300 mg. in saline, was given intravenously on two successive days. Bleeding had stopped on March 11, 1949, and the protamine titration was normal. During one of the injections of toluidine blue, some of the material infiltrated the tissues at the site of injection. No slough occurred but a painful cellulitis persisted for several days. Discoloration persisted only for a few hours. No blood was given.

CASE 9.—B. G., aged 40 years, No. 81911, had a complete hysterectomy on Feb. 7, 1949, with no excessive bleeding at operation or postoperatively until Feb. 26, 1949, at which time she had a massive vaginal hemorrhage. The protamine titration was elevated and protamine sulfate intramuscularly every six hours was started. Bleeding was reduced to spotting on Feb. 28, 1949, and had entirely stopped on March 1, 1949, at which time the titration was normal and protamine sulfate was discontinued. Another vaginal hemorrhage occurred on March 2 and although the protamine titration was still normal, 300 mg. of toluidine blue in 500 ml. of normal saline were given intravenously and this dose was repeated the following day. The titration remained normal and there was no further bleeding. The patient received two 500 ml. transfusions of whole blood on March 2 and March 4, 1949.

Comment

There is a bleeding and coagulation abnormality in certain cases of obstetrical and gynecological bleeding which temporarily responds to the administration of toluidine blue and/or protamine sulfate. The implication of the therapeutic response in relation to the pathogenesis of the bleeding has been

discussed elsewhere.[4] In some respects this bleeding abnormality is heparin-like in character, but it is not necessarily due to heparin. It may be detected by the protamine titration. Allen and co-workers[1] have indicated that such defects can be produced by substances other than heparin, and clotting disturbances of this nature (i.e., that respond to the parenteral administration of protamine sulfate or toluidine blue) may occur when the whole blood clotting time is entirely normal.

It should be pointed out that there are many causes of postpartum hemorrhage. These include: (1) retained placental tissue, (2) uterine atony, (3) lacerations, (4) tumors, (5) conditions of the blood such as thrombocytopenia, excessive fibrinolysins, hypoprothrombinemia and fibrinogenopenia.

Cases have been presented which indicate that if the above-mentioned abnormality is present as evidenced by an increased protamine titration, and other causes for bleeding have been ruled out, a clinical trial of protamine sulfate and/or toluidine blue therapy is indicated. No ill effects from the use of protamine sulfate have been noted except muscular soreness at the site of injection; however, it must be injected deeply into the muscles. Transient nausea may occur in about 20 per cent of the patients receiving toluidine blue. When this dye is given intravenously, precautions must be taken that there is no extravasation and that the injection is given slowly. Toluidine blue has a more prolonged action than protamine sulfate.

In those cases demonstrating increased protamine titrations there was often, but not always, an increase in the whole blood clotting time. There was no predictable increase or decrease in the thrombocyte count or prothrombin level. In no cases was fibrin deficiency observed.

The presence of an increased protamine titration per se does not mean that the individual is going to bleed; however, in the presence of bleeding, an increased protamine titration is an indication for toluidine blue or protamine sulfate therapy.

The results of treatment are extremely difficult to evaluate. In hypermenorrhea, the patient's word must be taken for the amount of bleeding and the character of the response after therapy. In the cases demonstrating active bleeding, it is impossible to state definitely that bleeding would not have stopped spontaneously.

Summary

1. There is often an increased protamine titration in normal pregnancy before delivery which returns to normal early in the puerperium.

2. The presence of an increased titration does not predict abnormal bleeding in pregnant women at delivery or in the puerperium.

3. If an increased protamine titration is present in a bleeding patient in whom no other demonstrable pathological cause is present, clinical trial of protamine sulfate and/or toluidine blue is indicated.

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THE EFFECT OF HYSTERECTOMY ON CARCINOMA OF THE CERVIX

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THE enthusiasm for surgery is having a serious effect upon patients treated for malignant disease of the cervix. Evidence of that effect can be noted in recent tumor clinic admissions. The M. D. Anderson Hospital for Cancer Research accepts for treatment only indigent patients living outside Harris County; therefore, the census is derived from a rural population. The Methodist and Hermann Hospitals admit women living in and around the City of Houston in Harris County; hence the census of these hospitals is composed chiefly of women from the urban population.

The material assembled here serves to focus attention on the trend of treatment in a representative proportion of women in the State of Texas. The cases studied may be divided into three categories:

1. Those in whom cancer was not recognized at the time of primary treatment.
2. Those women who were subjected to inadequate treatment by virtue of the performance of simple total hysterectomy.
3. Those women in whom an elective supracervical hysterectomy was done for a benign lesion, and who later developed a "true carcinoma of the cervical stump."

Of a total of 380 patients with carcinoma of the cervix, there were 62, or 16 per cent, who developed malignant disease following hysterectomy. We have regarded those in whom the diagnosis of persistent cancer was established within a period of six months or less following the hysterectomy as indicative of those in whom surgery was inadvertently performed in the presence of a coexistent cervical cancer. A carcinoma of the cervix which appears a year or more after hysterectomy could have been present at the time of operation. However, if it is diagnosed within six months after surgery the operating surgeon must accept the responsibility of its presence at the time of operation. Some writers strongly contend that three years should be the dividing line between true carcinoma in the cervical stump and malignant disease present in the cervix at the time of hysterectomy. There were 23, or 6 per cent, of our patients who developed true carcinoma in the residual cervix by these criteria. The frequency of carcinoma in the retained cervix following amputation of the uterus, however, is no greater than that found in the cervix of an intact uterus. This has been proved and is widely accepted. This figure, therefore, is not to be interpreted as indicative of the frequency with which carcinoma of the cervical stump can be expected following subtotal removal of the uterus.

There were 10 (3 per cent) in whom there was probable persistent cancer in the cervical stump, because the diagnosis of malignancy was established within one to three years following hysterectomy. Definite cancer could be

demonstrated in the cervical stump of 16 patients, or 4 per cent, because the diagnosis was established less than one year postoperatively. Those in whom a *total* hysterectomy was performed and there was definite persistent cancer under one year numbered 13, or 3 per cent. In seven patients the total hysterectomy was done following irradiation. None of these patients showed evidence of a radical gland dissection. There were 3 patients in whom a total hysterectomy was performed and the presence of the cervical malignancy was not established until after surgery. Therefore, we see that of the 380 admissions for carcinoma of the cervix, there were 27 patients with active cancer treated surgically less than six months previously. *In other words, nearly one half of all patients who developed cancer following hysterectomy did so during the first six months following the operation.* On these patients, certainly, the surgeon operated in the presence of an existing cervical cancer.

TABLE I

	NUMBER	PERCENTAGE OF THOSE SUBJECTED TO HYSTERECTOMY	PERCENTAGE OF TOTAL NUMBER OF CARCINOMA OF CERVIX REVIEWED (380)
True cervical stump cancers (3 years or more postoperative)	23	37	6
Probable persistent cancer cervical stump (1 to 3 years postoperative)	10	16	3
Definite persistent cancer cervical stump (Less than 1 year postoperative)	16	26	4
Definite persistent cancer *without* cervix (Less than 1 year postoperative)	13	21	3
Total	62	100	16

These patients had visited their physicians promptly. Eighty-two per cent of our 62 patients sought medical aid within three months following the onset of irregular bleeding, which in retrospect should have been regarded as characteristic of a genital cancer.

TABLE II

Definite persistent cancer less than 1 year postoperative		29
Active cancer less than 6 months postoperative (Total and subtotal hysterectomy)	27	
Definite persistent cancer without cervix	13	
1. Purposely treated surgically	10	
a. Irradiation preceded hysterectomy	7	

Our material forces the conclusion that any candidate for consideration of a hysterectomy must be critically surveyed before she is admitted for surgery. The history of irregular bleeding, regardless of age, demands explanation. Contact bleeding should always draw one's attention to the cervix. The age of the patient is of relative value in that malignancies of the endometrium are more likely to occur in the older age group. Principle reliance, however, rests on an accurate pelvic examination. If, on inspection, a suspicious area on the cervix is noted, a biopsy is indicated. Vaginal and cervical smears can be done but only for screening purposes. Final decision demands histological study of paraffin-embedded tissue by a competent pathologist. The time necessary for this is well spent, and even though the presence of a malignancy is the ultimate diagnosis, an accurate outline of therapy can then be more reasonably developed.

One need have no fear of spreading the malignancy. Even assuming such a possibility the exigency of a proper diagnosis far outweighs any possible disadvantages from this trauma. An endometrial biopsy curettage can be utilized to explore the endocervical canal and the uterine cavity itself. Here again the advantages of an established diagnosis with full knowledge of the point of origin of the malignancy cannot be overemphasized.

TABLE III

SYMPTOMS NOTED BEFORE VISITED PHYSICIAN	NUMBER	PER CENT
3 months or less	50	82
4 to 7 months	4	6
7 months to 1 year	3	5
Over 1 year	3	5
History failed to state	1	2
Total	61	100

A fractional curettage is indicated when the point of origin of the tumor cannot be definitely determined by office procedures. Biopsy of the cervix can be effectively accomplished by sharp dissection of the ring of tissue marking the junction of squamous and columnar epithelium at the external os of the cervix. Conization of the cervix is of little value, since it sears the tissue and makes histological examination difficult. The endocervix should be explored with a small curette to prove the presence or absence of malignant change. Finally, the uterine cavity is explored; all materials are labeled separately and sent to the laboratory.

In the presence of a benign cervical lesion, statistical analyses are of variable value in proving the advantages of elective total hysterectomy, over the supposedly less hazardous supravaginal amputation. It would seem more appropriate to advocate a total removal of the uterus when there is no contraindication to such a procedure. Most gynecologists prefer to do a total hysterectomy when the technique is feasible. We see no reason for condemnation of such practice. There is no justification for interdicting a procedure because the average surgeon cannot carry it out properly. However, if one does a partial hysterectomy without a previous positive diagnosis, the uterus should be opened before the final decision is made to leave the cervical stump.

Those patients presenting indisputable evidence of persistent tumor within a year following hysterectomy have generally been operated upon by supravaginal removal of the uterus because the doctor did not look for cancer in the cervix. It should be kept in mind that the mortality rate of cervical carcinoma is second only to that of breast carcinoma in women 35 to 55 years of age. Removal of the uterus has been done on some occasions because the doctor apparently felt that no help was to be obtained from irradiation. Such physicians have no appreciation of the developments in modern irradiation techniques. On the other hand, there are patients who have been treated by ineffective irradiation therapy and then have been subjected to hysterectomy in a futile attempt to save their lives. The ineffectiveness of such surgery becomes clearly evident within a few months, when a patient with a large pelvic mass causing pain from pressure on great nerve roots is turned over to the radiotherapist.

Mindful of the dissemination of recent advances in cancer treatment, authors should be more specific in their definition of adequate surgery and irradiation techniques when publishing end results. The whole problem of treatment in genital cancer depends on adequate utilization of every means in our therapeutic armamentarium. Our future progress lies in the synergistic adaptation of our knowledge of both surgery and irradiation. These two means of treatment are

complementary rather than antagonistic. We must not lose our gains in either of these branches of medicine which have been laboriously consolidated by many great students of this problem. The arguments indulged in by so many of our great teachers in both of these medical specialties are interpreted by the average clinician as indicative of treatment trends. The debate between the proper sequence of x-ray, radium, and surgery must not be misconstrued to mean the average surgeon has a prerogative to assume nothing can be done and so any means of therapy at hand is justified because the ill result will obtain, regardless. Broad general statements such as "the patient was treated by irradiation" are of no value in the correlation of results.

During the past 25 years radiotherapeutic clinics in the United States and abroad have consistently reported a relative cure rate of 28 to 40 per cent in carcinoma of the cervix. This represents the advance in radiotherapy and greater effort should be made to emulate these examples in order to form a foundation on which to build modern surgical techniques. One may as well condemn all cooking because most people are not good cooks, as to discount blandly irradiation therapy in cervical carcinoma. One big reason for the general discouragement in radiotherapeutic results lies in the dearth of true clinical radiotherapists. All too frequently radium and x-ray are administered in a stereotyped fashion by one who is not particularly interested either in the biological response in the patient as a whole, or in the particular tumor. Biological variations are allowed for in every branch of medicine, radiotherapy is no exception. If this were not true, the nuclear physicist could prescribe the therapy and the physician could be dispensed with.

Summary

Carcinoma of the cervix has been studied in three Houston hospitals to furnish material from urban and rural areas. Hysterectomy was associated with a mistake in diagnosis in one group of women; it represented elective surgery as a primary means of therapy in a second group; and in the third group the hysterectomy was performed for a benign uterine lesion and the true carcinoma of the cervix followed three or more years later. It has been shown by our review that far too many of these patients had definite evidence of tumor six months or less following surgery. Emphasis should be placed on the fact that when surgery is the procedure of choice, it must usually include a radical gland dissection to be of value. Accurate diagnosis of pelvic disease involves the physician's ability to recognize a cancer where one exists. In addition, the clinician is charged with the responsibility of tracing the neoplasm to its point of origin.

Appreciation of the biological variations in tumors prior to, during, and after treatment demands wise clinical judgment in evaluation. The person who administers ionizing radiation must be as sound a clinician as are those who practice surgery. Radiotherapy as well as surgical therapy requires the doctor's ability to alter technique as circumstances differ. Consequently, the doctor must have a thorough understanding of the fundamental principles of both types of therapy in order to eradicate the individual tumor.

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QUANTITATIVE ESTIMATION OF MONAMINE OXIDASE IN THE PLACENTA IN NORMAL PREGNANCY AND TOXEMIA*

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PLACENTAL dysfunction is considered by some workers as a possible factor in the etiology of toxemia of late pregnancy.[1] This paper reports an experimental approach to this theory in terms of enzymatic function of the placenta.

In a previous paper, the author, in collaboration with H. O. Singher,[2] established the presence of monamine oxidase in the placenta. This enzyme was selected for study because it catalyzes the oxidative deamination of many sympathomimetic amines,[3] and thereby abolishes their vasopressor effect.[4] Among the amines attacked by this enzyme, namely, epinephrine, oxytyramine, tyramine, etc., the latter has been held to induce the hypertension of toxemia.[5] Evidence exists for the limitation of enzymatic activity by anoxic conditions. The activity of monamine oxidase is known to be proportional to oxygen tension.[6] Further, enzymatic activity is reduced in the ischemic kidney of dogs with experimental hypertension.[7] Since placental ischemia has been advanced as a possible etiological factor in toxemia,[8] the question arose whether the activity of monamine oxidase and concomitant inactivation of pressor amines in the placenta may be reduced in this disease. The quantitative estimation of monamine oxidase in the placenta in normal pregnancy and toxemia presented in this paper gives an answer to this question.

Methods

The detailed experimental technique for the assay of monamine oxidase in the placenta is described in a previous paper.[2] The principle of the technique is measurement of oxygen consumption of placental homogenate in the Warburg apparatus under partial exclusion of secondary oxidations and subsequent determination of ammonia by Conway microdiffusion method. Tissue nitrogen determinations were carried out on the homogenate in each experiment.

Results

The results are presented in the table. A total of seventy placentas were assayed and grouped according to clinical findings. The mean nitrogen content of the tissue samples used for the assay is given for each group, since the calculation of the enzymatic activity is based on these values. The enzymatic activity of monamine oxidase is expressed as $Q_{O_2}(N)$ and $Q_{NH_3}(N)$, i.e., mm.[3] of oxygen or ammonia per hour per mg. tissue nitrogen. This allows a direct comparison between the oxygen consumption and the ammonia formation during the deamination. The theoretical ratio for the experimental conditions chosen is:

$$\frac{2\ Q_{O_2}(N)}{Q_{NH_3}(N)} = O/NH_3 = 1.00 \quad (2)$$

The experimental ratios found are given in the last column.

In 30 cases the placentas came from normal full-term pregnancies (term by weight of baby and calculated duration). In this series the enzymatic activity expressed as its mean $Q_{O_2}(N)$ equals 17.8 ± 3.54. The parity, age of the mother, weight of placenta, type of anesthesia were without influence. No correlation was found between the $Q_{O_2}(N)$ and fetal distress intrapartum or asphyxia neonatorum. In two instances normal values were found in placentas in cases where the fetus had died in utero less than one week before labor. In one of these cases the death was due to cord strangulation, in the other the cause was unknown. There was also no correlation between the enzymatic activity of the placenta and the histological changes in this organ at term as manifested by various degrees of hydropic degeneration, hyalinization, infarction, or fibrosis.

TABLE I. MONAMINE OXIDASE ACTIVITY IN THE PLACENTA

SOURCE OF PLACENTA	TOTAL CASES	NITROGEN PER 0.5 GM. OF TISSUE		$Q_{O_2}(N)$			$Q_{NH_3}(N)$			RATIO O/NH$_3$		
		MEAN S. D.	C. V.	MEAN S. D.	C. V.		MEAN S. D.	C. V.		MEAN S. D.	C. V.	
		mg	%	mm³/hour/ mgN	%		mm³/hour/ mgN	%			%	
Normal term pregnancy	30	7.52 ± 0.83	11.0	17.81 ± 3.54	19.9		34.42 ± 7.40	21.5		1.04 ± 0.088	8.46	
Toxemia of late pregnancy	18	7.81 ± 0.67	8.6	16.6 ± 3.3	19.9		31.7 ± 5.6	17.7		1.04 ± 0.07	6.7	
Complicated pregnancy	22	7.05 ± 1.20	17.0	17.8 ± 4.99	28.1		33.5 ± 8.49	25.4		1.05 ± 0.098	9.32	

In 22 cases the placentas were obtained from patients with complications of pregnancy, namely: 4 from patients with premature labor, 1 from a therapeutic abortion at 16 weeks, 2 from severe diabetics, 8 from patients with syphilis, 2 from patients with pulmonary tuberculosis, 2 from patients with premature separation of a normally inserted placenta with retroplacental hematoma, 2 from patients with anemia, 1 from a patient with two years' amenorrhea preceding pregnancy. The $Q_{O_2}(N)$ for the placentas with abruptio were 21.4 and 14.0, respectively. Both cases of anemia gave low values. However, the mean $Q_{O_2}(N)$ of this series is the same as for normal pregnancy, only its coefficient of variation is higher, 28.1 per cent compared to 19.9 per cent. This large variation is due to a greater variation of the tissue nitrogen content in this series which shows a coefficient of variation of 17 per cent as against 11 per cent for the placentas from normal pregnancy.

The enzymatic activity of monamine oxidase in 18 cases of toxemia of late pregnancy expressed as it means $Q_{O_2}(N)$ equals 16.6 ± 3.3.* The coefficient of variation is 19.9 per cent, the same as for normal pregnancy. There was no correlation of the $Q_{O_2}(N)$ in toxemia with the severity and/or the duration of the disease. It is evident that there is no significant difference in the activity of monamine oxidase in the normal placenta and that from patients with toxemia. This holds true whether the enzymatic activity is calculated on the basis of wet weight of tissue or of tissue nitrogen.

In all three series there is an excellent agreement between the oxygen uptake and the ammonia production. The observed mean ratios of 1.04, 1.04, and 1.05 are very close to the theoretical O/NH$_3$ ratio of 1.00. The coefficient of variation is less than 10 per cent. These figures prove the validity of the method used for the assay.

*In this series all standard deviations are calculated by the formula S.D. $= \sqrt{\Sigma d^2/n-1}$, since there are less than 20 observations.

The average nitrogen content of 0.5 Gm. of wet weight of placental tissue is 7.5 mg. It follows that an average placenta of 500 grams with a $Q_{O_2}(N)$ of 17.8 can theoretically deaminate 1.6 Gm. of tyramine per hour. The role of this enzyme in the placenta is in all likelihood the same as in other organs, detoxification of amines. Therefore, the conclusions seem justified that this particular placental function is not altered in toxemia.

Summary

The activity of monamine oxidase was assayed in the placentas from normal pregnancy and toxemia of late pregnancy. The enzymatic activity is not changed in toxemia. The conclusion is drawn that the ability of the placenta to inactivate sympathomimetic amines by deamination is not altered in toxemia.

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A NEW SIMPLE METHOD OF FETOMETRY IN BREECH PRESENTATIONS

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A BORDERLINE pelvis in a breech presentation presents one of the most difficult problems which an obstetrician must face. If he overestimates the relative size of the vertex, he may do a cesarean section which is unwarranted; if he underestimates the relative size of the vertex, the fetus may be lost at the time of delivery. In a recent article Seeley[1] has aptly stated, "The existence of cephalopelvic disproportion, then, is often not discovered until late in the second stage of labor when the child is seriously endangered from asphyxia or from urgently indicated attempts at delivery. The seriousness of this complication as a factor in breech presentation is evident from various reports."

Recognizing the above-mentioned difficulties, the authors set about to devise a method of cephalopelvic measurement in breech deliveries which would be simple enough to be used in any modern laboratory and which could be readily interpreted by the obstetrician. We felt that any method which did not meet these requirements would have only a limited value in solving the problem of cephalopelvic disproportion in breech cases. Various methods have been devised for measuring the fetal head, some of which are applicable to breech deliveries. No effort will be made to review completely the literature on this subject as Dippel and Delfs[2] in 1941 have given an excellent review and Torpin[3] more recently has also done so. It will be mentioned, however, that as early as 1931 Thoms[4] used a modified grid technique to measure the fetal head. This method could have been applied to breech presentations. In 1940[5] he modified this technique to measure the suboccipitobregmatic circumference rather than the occipitofrontal diameter. The suboccipitobregmatic diameter, however, was not measured. Walton[6] in 1931 and Clifford[7] in 1934 also devised satisfactory methods of fetometry, but both required anteroposterior and lateral films and were thus subject to considerable error from fetal movements. Scarpellino[8] modified the above technique in breech presentation by placing the patient in the posterior-anterior position, thereby bringing the fetal head closer to the film. Ball and associates[9, 10, 11] applied the teleroentgenographic procedure for volumetric determination of both the fetal head and the pelvis. In the latest of these they have recommended that the x-rays be made with the patient standing to keep the fetal head relatively fixed. This method is accurate enough but is complex, requires a well-trained technical team, and when final tabulations are completed gives results in total volumetric determinations. The suboccipitobregmatic diameter which is the most significant one is not calculated. Guerriero, Arnell, and Irvin[12] after the study of a small series of cases by this method came to the conclusion that this method was not very accurate in breech presentations.

Dippel and Delfs[2] prefer stereoscopic visualization, which certainly is a very accurate method. This, however, requires two exposures without movement of the fetal head and in addition requires meticulous technique. Torpin and Allgood[3] using the isometric technique have advised placing the patient in a lateral position, palpating the fetal head, then placing a metal marker over its center. It has been our experience in breech presentations with the patient in a lateral position that the fetal head drops to one side, which makes the head very difficult to outline and may lead to inaccurate placement of the lead scale.

In 1944 Colcher and Sussman[13] devised a simple isometric technique for pelvimetry and fetometry which required a minimum of apparatus, was simple to film, and in addition incorporated a new principle of intersecting diameters for measurement of the pelvis. This method because of its simplicity was easily interpreted by the obstetrician and gave him measurements which could be readily applied clinically. This method was adopted successfully at the Crawford W. Long Memorial Hospital. We modified this technique for measurement of the vertex in breech presentations so that the centimeter graduated ruler is placed beside the fetal head using much the same technique as Thoms[4] has described for the measurement of the fetal head in vertex presentations.

Technique for Filming

The patient is placed upon the x-ray table in the recumbent position (Fig. 1). The fetal head is palpated and the Colcher-Sussman ruler is placed on the side of the abdomen closest to the fetal head. In the average-sized woman the ruler should be placed 6 cm. below the anterior abdominal wall at the level of the fetal head. In the obese woman the ruler should be dropped to 7 cm. below the abdominal wall. An anode-film distance of 36 inches was used in the first ten cases but this was increased to 40 inches in the last forty cases as it proved to be more accurate. The tube in directed so that the central ray passes through the fetal skull. The fetal head is thus filmed in the same plane as the ruler. The usual technique for filming is used, the average being about 85 kv. and 240 Ma. per second. One 8 by 10 film is required in most cases. The suboccipitobregmatic or biparietal diameter of the fetal head is measured by calipers and the true diameter obtained from the image of the ruler on the film. In measuring the fetal head the calipers should be placed upon the outermost portion of the white line which represents the periosteum of the fetal head.

The patient is not removed from the table until the first film is developed. If the wet film reveals the fetal head to be in an oblique position of more than approximately 25 degrees from either the true anteroposterior or true lateral, an abdominal binder is applied as shown in Fig. 2. This binder is applied directly over the fetal head and is drawn as tightly as possible. A second film is then taken. It was found in most instances that pressure applied by the binder would tend to convert the fetal head from the oblique into either the anteroposterior or lateral position so that proper measurement could be taken. The premature head could seldom be converted, probably because of the proportionately greater quantity of amniotic fluid. However, since cephalopelvic disproportion is rare when the infant is premature, this is not a significant detail.

Technique for Measurement

The biparietal diameter is readily measured from the film when the fetal head lies in the sagittal plane. This diameter is also easily measured in the living infant. The suboccipitobregmatic diameter is more difficult to measure because the proper point in the suboccipital region is difficult to locate.

Stander[14] placed this at the "under surface of the occipital bone just where it joins the neck." Since there is a large amount of soft tissue in this region which is not visualized by x-ray, we have adopted an arbitrary landmark.

The occipital protuberance is easily palpable in the living subject and is readily visible in the x-ray film. We have, therefore, measured from a point immediately below the occipital protuberance to the midportion of the anterior fontanelle, which point is readily visible and equally as readily palpable.
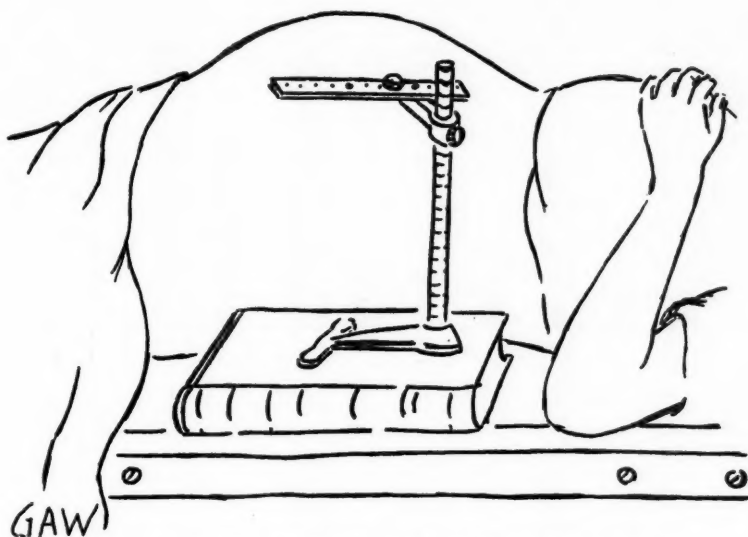
Fig. 1.—Sussman ruler properly placed for first film.

Fig. 2.—Abdominal binder applied to rotate fetal vertex from an oblique view.

In measuring the vertex of the delivered infant a standard Martin or similar pelvimeter is used. Firm pressure is applied when measuring the suboccipito-bregmatic diameter to allow for bulging of the fontanelle and for soft tissue displacement. Because of this pressure we do not subtract for soft tissue over the periosteum as some have suggested.

TABLE I

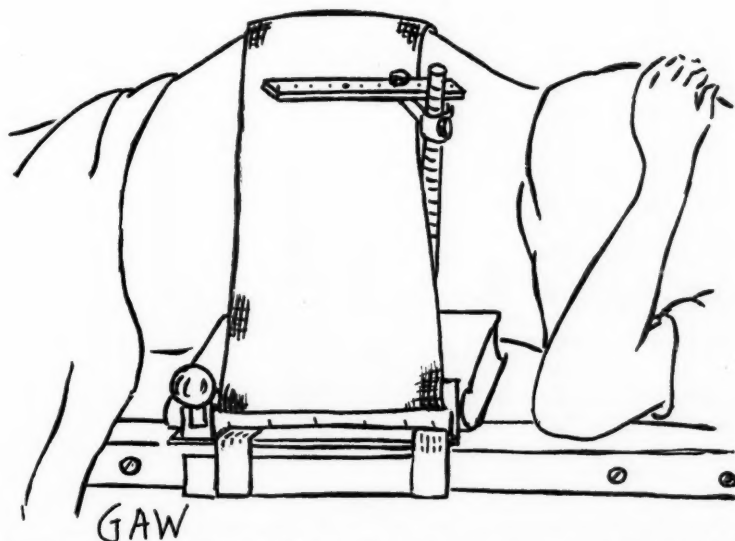| PATIENT	ANODE-FILM DISTANCE	SUBOCCIPITOBREGMATIC DIAMETER			BIPARIETAL DIAMETER		
		BIRTH (CM.)	X-RAY (CM.)	DIFFERENCE (CM.)	BIRTH (CM.)	X-RAY (CM.)	DIFFERENCE (CM.)
J. C. D.	36	9.65	9.25	0.40	9.25	–	–
P. H. R.	36	10.00	10.10	0.10	–	–	–
T. C.	36	10.00	9.80	0.20	9.80	–	–
A. H. M.	36	10.00	9.20	0.80	9.20	–	–
H. L. S.	36	11.00	10.20	0.80	–	–	–
L. R. P.	36	9.75	9.75	0.0	9.50	–	–
B. N. G.	36	8.80	8.80	0.0	8.50	–	–
R. K. R.	36	10.70	10.25	0.45	9.80	–	–
H. L. M.	36	9.75	9.00	0.75	8.90	–	–
H. L. M.	36	9.50	9.10	0.40	8.90	–	–
M. O. S.	40	9.25	9.25	0.0	9.50	–	–
W. E. L.	40	10.20	9.40	0.80	9.60	–	–
O. A. W.	40	9.50	9.00	0.50	9.0	–	–
G. T. C.	40	10.10	10.20	0.10	9.0	–	–
B. C. W.	40	10.50	10.50	0.0	10.0	–	–
G. T. M.	40	9.00	9.30	0.30	9.0	–	–
J. O. S.	40	10.00	10.00	0.0	10.0	–	–
J. H. W.	40	9.6	9.1	0.50	8.8	–	–
A. M. D.	40	9.25	9.25	0.0	9.0	–	–
C. E. C.	40	8.40	8.40	0.0	7.9	–	–
W. E. W.	40	9.10	9.10	0.0	8.4	–	–
W. C. S.	40	10.00	10.30	0.30	9.1	–	–
H. M.	40	8.98			8.20	8.15	0.05
W. J. H.	40	9.8	9.7	0.10	9.2	–	–
G. T. L.	40	9.25	9.30	0.05	9.9	–	–
A. L. E.	40	9.20	9.30	0.10	9.0	–	–
A. W. J.	40	9.75	9.60	0.15	9.1	–	–
S. M. R.	40	9.9	10.10	0.20	9.1	–	–
C. E. M.	40	9.5	9.5	0.0	8.9	–	–
F. N. D.	40	10.1	10.00	0.10	9.5	–	–
H. F. N.	40	8.9	8.9	0.0	8.5	–	–
P. R. W.	40	10.0	10.0	0.0	9.5	–	–
D. M. P.	40	9.2	9.0	0.20	9.0	–	–
J. F. T.	40	9.0	8.8	0.20	–	–	–
R. J. P.	40	9.5	9.4	0.10	–	–	–
B. A. W.	40	10.15	10.25	0.10	9.9	–	–
H. M. B.	40	9.0	8.9	0.10	8.9	–	–
M. F. H.	40	9.4	9.4	0.0	8.5	–	–
J. I. H.	40	9.3	9.1	0.20	9.0	–	–
R. Mc.	40	9.5	9.5	0.0	8.2	–	–
J. E. L.	40	9.8	9.8	0.0	9.25	–	–
M. W. G.	40	9.3	9.4	0.10	8.2	–	–
R. C. C.	40	10.0	9.9	0.10	9.3	–	–
T. T. G.	40	9.7	9.9	0.20	9.0	–	–
A. L. S.	40	9.9	10.3	0.40	9.3	–	–
C. H. H.	40	10.0	9.9	0.10	9.1	–	–
W. A. B.	40	9.8	10.1	0.30	8.5	–	–
L. S.	40	10.1	10.3	0.20	9.0	–	–
L. S.	40	10.0	9.7	0.30	9.2	–	–
H. D. B.	40	9.5	9.5	0.0	8.9	–	–

Material

Using the technique above described, 50 private and charity patients with breech presentations were filmed prior to delivery at the Crawford W. Long Memorial Hospital. No effort at selectivity was made, large and small women alike being included. There were two sets of twins. In each instance the first twin was presenting by breech. Most of these films were taken when the patient was in early labor. None was taken more than three days before the onset of labor. Errors due to fetal growth were thus minimized. The sub-

occipitobregmatic measurement was made from the film and the results recorded. Following the delivery of the infant the same measurements were made on the delivered child and recorded so that the two measurements could be compared. These measurements were made by different observers.
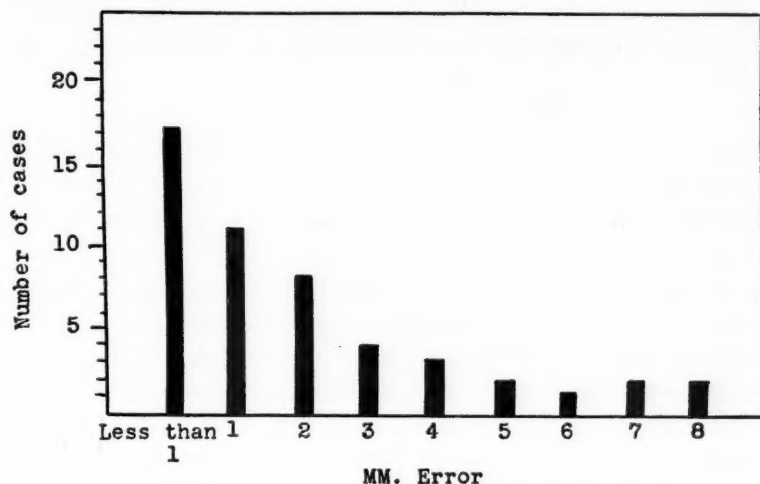
Fig. 3.—All fifty cases studied, the first ten using a 36-inch anode-film distance and the remaining forty cases using a 40-inch anode-film distance.
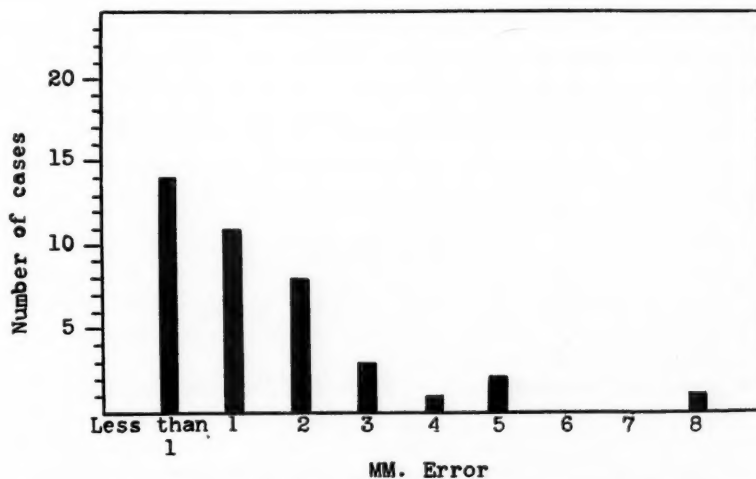
Fig. 4.—Last forty cases studied using a 40-inch anode-film distance.

Results of Measurement and Discussion

Table I gives a complete résumé of the clinical and x-ray findings of the entire series. Fig. 3 represents these cases in graphic form. Along the abscissa the quantity of error is shown in millimeters, i.e., the difference between the measurement of the suboccipitobregmatic diameter on the film and that found when the delivered infant was measured. Along the ordinate is listed the number of cases involved in each category. Fig. 4 constructed in the same manner represents the last forty cases, all of which were filmed at 40 inches instead of 36 inches anode-film distance. This is done to show the more accurate results obtained by the latter technique.

Torpin[3] has concluded from a study of 482 cases that a 5 per cent error is the minimum which can be expected in the measurement of the newborn's head. The average measurement of the suboccipitobregmatic diameter of these fifty cases was 9.64 cm. A 5 per cent error would be 0.49 cm. or approximately one-half (0.5) cm. It can be seen from a study of Fig. 4 that only one of these cases had an error in measurement of greater than 0.5 cm. A review of this film revealed the head to be in an oblique position.

Summary and Conclusions

1. A new isometric technique for the measurement of the fetal head in breech presentation is described.

2. The technique of the method is simple. A minimum of apparatus is required and interpretation is rapid and easy.

3. The suboccipitobregmatic or biparietal diameter is measured, thus giving the obstetrician measurements with which he is most familiar and which are at the same time of the greatest clinical significance.

4. Results of the method to date indicate that unless the head is fixed in an oblique position it can be measured to within 0.5 cm. in any patient and in most instances to within 0.3 cm., which is accurate enough for clinical evaluation of cephalopelvic disproportion.

5. An abdominal binder technique is described which can be used in oblique positions of the fetal vertex to rotate it into an anteroposterior or lateral position for more accurate measurement.

6. Using the above described technique for fetometry and the usual Colcher-Sussman technique for pelvimetry it is possible to gain an accurate estimate of cephalopelvic relationships in breech presentations.

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THE EFFECT OF GYNECOLOGIC SURGERY ON SEXUAL REACTIONS*

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THIS presentation is the result of a ten-year study in which private patients who had undergone gynecologic operations were questioned as to the effect of surgery upon their sexual reactions. It was undertaken because it seemed that considerable confusion beset the laity (and some within the profession) as to the relationship between the genital organs and the sexual reactions in women. This has been most evident when a patient, upon being told that she requires gynecological surgery, expresses serious fears as to its effect upon her sexual urges and her ability to culminate coitus in a climactic orgasm. As a reult of this survey it has been possible intelligently to tell the woman who is to undergo pelvic surgery what changes, if any, she may expect in her sexual life subsequent to operation. Three groups of patients were interrogated: those who had had all ovarian tissue removed; those who had had a complete hysterectomy, either abdominal or vaginal but who had retained ovarian tissue; and three women in whom the clitoris had been excised.

The first group of women questioned had undergone abdominal complete hysterectomy with bilateral salpingo-ovariectomy. There were sixty-eight women in this group all of whom had had preoperative sexual experiences. The youngest was 26, the oldest 43 years of age. At the time of questioning in all cases at least one year had elapsed since surgery. Thirty-four of the patients had been operated upon three or more years prior to questioning. Fifty-eight were on some form of estrogenic therapy. Each women was asked whether her sexual reactions were the same after surgery as before. Sixty-one replied in the affirmative. Two who had sexual urges and occasional orgasms prior to operation, did not experience any sexual reactions subsequent to operation. Both stated that prior to surgery they had been extremely apprehensive lest they lose their sexual desire. The remaining five women had experienced normal sexual reactions and orgasms in the past but had lost their normal urges as a result of dyspareunia of organic origin. Normal sexual reactions were regained after extirpation of pelvic pathologic processes which removed the cause of their dyspareunia.

Eighty-six women were questioned who had had either vaginal or abdominal complete hysterectomy without removal of the ovaries or uterine tubes. All had had previous sexual experiences. The age of the youngest was 31, the oldest 49 years. Eleven of the women in the older age group were

taking some form of estrogenic therapy for menopausal symptoms. At the time of questioning one year or more had elapsed since surgery in all cases. Seventy-seven stated that their sexual reactions were unchanged; one suffered a loss of sexual urge and orgasm and three (with organic cause for dyspareunia which was removed by surgery) had a return of normal sexual reactions after operation.

The one patient who suffered a loss of her sexual reactions after vaginal hysterectomy was an unmarried woman who had invariably associated pregnancy with coitus, and who insisted upon reassurance that removal of the uterus (removed because of myomas) would eliminate the possibility of pregnancy.

There were three cases in each of which the clitoris had been removed as part of a vulvectomy performed for kraurosis and leucoplakia. These women continued to have coitus after operation. In one, a 47-year-old married woman whose leucoplakic lesion was limited to the folds about the clitoris, only that organ and a small portion of the anterior vulva were excised. She had had moderate sexual urges and experienced an occasional orgasm before operation. The procedure did not affect her sexual reactions. The other two were 53 and 56 years of age, respectively. Both still had coitus, neither had had any sexual urge or orgasm for a number of years before surgery and neither reported any change after operation.

Psychological explanations of the phenomena of sexual drive and the orgasm leave much to be desired. According to Deutsch,[1] the motives which drive man and woman to the sexual act are tremendously different. The somatic urges in the male which are gratified by the emptying of distended genital organs during copulation do not exist in the female. Her urges are not manifestations of a physical dissatisfaction but are rather erotic yearnings, a narcissistic need to be loved and a masochistic striving to give. It is Allport's[2] hypothesis that the original sex stimulus is not a psychological phenomenon aroused by an individual of the opposite sex, but is rather an internal excitant presumably of hormonal origin. Allport states that in the female the excitatory visceral changes are probably caused by some endocrine process associated with the menstrual cycle. The anatomical location of sexual excitation in the female has not been determined. During adolescence the clitoris is the center of sexual excitation. Freud assumed that in maturity the vagina took over the erotic sensations of the clitoris. It is Deutsch's opinion, however, that the vagina usually becomes the center of spontaneous sexual excitation only in women who have had direct sexual experience and that in women who have not had such experience the clitoris remains the center of sexual excitability.

Much less is known about the psychological and physical processes occurring during the female orgasm than is known of the same phenomenon in the male. In the male, as a result of sexual excitation, engorgement of the genital organs occurs; physical contacts stimulate somatic sensory end organs in the genitals which produce spasmodic contractions of the musculature of the accessory sexual glands and ejaculation occurs. With the ejaculation there is a discharge of retained secretions which are accompanied by a sense of gratification, satisfaction, and release, followed by a period of somatic relaxation. In the female the somatic urge to discharge retained secretions is not comparable to that in the male. Psychological factors undoubtedly are more important in conditioning her for an orgasm. The mechanism of the orgasm, however, is

apparently the same. Sexual stimulation increases engorgement of the genitals; as a result of physical contact vaginal sensory organs are stimulated. These stimuli produce vaginal contractions and spasmodic muscular movements which culminate in a phenomenon comparable to the male orgasm but without the discharge of retained secretions.

It is hazardous to draw more than philosophical conclusions from the questioning of patients about something as ephemeral as their sex life. This study, however, would tend to bear out the assumption that the vagina becomes the center of normal sexual activity in the mature female. Removal of the entire uterus, removal of all ovarian tissue, and, in one instance, removal of the clitoris did not change the sexual reaction in women who had experienced coitus prior to operation. In several instances normal sexual responses, lost as a result of dyspareunia due to organic disease, returned following removal of the ovaries or uterus and correction of the lesions producing the dyspareunia.

From the foregoing certain conclusions may be drawn with some degree of probable accuracy. It appears that neither the physiologists nor the psychologists are, as yet, prepared to give us definite opinions as to the nature of sexual reactions in women. From the questions asked a group of private patients it seems that the physician can, with only slight reserve, tell the woman who is to undergo hysterectomy and/or bilateral ovariectomy that her sexual life after operation will follow the same pattern it did before.

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EFFECT OF ADDITION OF SPERMATOZOA ON THE SUGAR CONTENT OF CERVICAL MUCUS

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THE study herein described had its incipiency in the following considerations: (1) spermatozoa require sugar for their prolonged metabolism[1, 2, 3]; (2) sugars, supplied by the seminal vesicles, are present in the ejaculate to the extent of about 300 mg. per cent[4, 5, 6]; (3) semen on standing suffers a diminution of sugar.[7] Individual spermatozoa, in pursuing their way through the cervical mucus, leave their original environment and presumably carry with them little extracellular nutrient material. Their new environment, i.e., the cervical mucus, significantly also contains various sugars[8, 9, 10] in quantities comparable to those found in the ejaculate. Glycogen in the female genital tract has been regarded as important in maintaining ovular life.[11] Whatever else their established functions are, one may hypothecate that the potential reducing substances in this tract are utilizable by spermatozoa as suggested by MacLeod[3] and Hughes.[11] However, such scheming is subject to hazards with which those who have seen their favorite bubbles grow and burst are familiar. Aware of potential pitfalls, the authors undertook this study to determine the effect of the addition of washed spermatozoa on the sugar content of cervical mucus.

Methods

Specimens of cervical mucus were obtained from sixteen healthy women ranging in age from 19 to 30 years. Nine of the subjects were unmarried. All were nulliparous, and had normal pelvic structures and menstrual cycles. Specimens were collected once daily, save during menstruation, and on successive days, when possible. All the mucus was withdrawn from the cervical canal by gentle suction with a glass cannula after the external os had been wiped clean. The specimens were promptly transferred to clean test tubes and accurately weighed. During the preovulatory and postovulatory phases the amount of secretion is scant, and at these times less than 10 mg. may be obtainable at a single collection. During the ovulatory phase, however, when production is copious, more than 1 Gm. of material may be aspirated. The menstrual cycles of all subjects were recorded and individual mucous specimens arbitrarily assigned to the preovulatory, the ovulatory, and the postovulatory phases.

Semen was obtained from healthy donors, house officers and medical students, by manual stimulation. The sperm counts ranged from 67 to 262 million, and averaged 130 million per cubic centimeter. Following liquefaction, and usually within two hours, 1.0 c.c. of the semen was added to 5 c.c. of Ringer's solution and centrifuged at 1,500 r.p.m. for 10 minutes. The supernatant was withdrawn, and the spermatozoa resuspended in Ringer's solution so that 0.1 c.c. of the suspension contained 1 million spermatozoa.

The cervical mucus was subjected to determination of total reducing sub-
stances by the method of Somogyi.[12] Because the mucus is not homogeneous,
division of the specimens into aliquots was impractical. For this reason, indi-
vidual specimens were analyzed in their entirety. A total of 285 specimens was
studied. Of these, 133 were immediately hydrolyzed, and the amount of total
reducing substance determined. Seventy-seven specimens were placed in stop-
pered test tubes, and stored at room temperature, i.e., 23 to 26° C., for twenty-
four hours before hydrolysis. Seventy-five specimens were allowed to stand
under similar conditions for twenty-four hours after admixture with washed
spermatozoa in the amounts of 1 million per 100 mg. of mucus. For purposes
of control, the samples of washed spermatozoa, containing 1 million per 0.1 c.c.,
were similarly handled and analyzed for total reducing substance after twenty-
four hours. The correction factor thus derived was subtracted from the result
obtained from the analysis of the mucus-washed spermatozoa mixture after it
stood for twenty-four hours, and appropriately regarded in the final tabulations.

Results

In a previous communication, the authors[7] reported on the effects of in-
cubation on the total reducing substances in 276 mucous specimens. Since that
time, further data based on 285 additional specimens have accumulated. The
over-all results from both groups of data are comparable to those already reported
and add credence to the observation that the amount of total reducing substances,
regarded as sugar, suffers a distinctly appreciable diminution on standing. As
indicated in Table I, this decrement amounts to 5.62 per cent, 20.4 per cent,
and 10.1 per cent in the preovulatory, ovulatory, and postovulatory specimens,
respectively.

TABLE I. SHOWING THE AMOUNTS OF TOTAL REDUCING SUBSTANCE, AS SUGAR, RECOVERED
FROM CERVICAL MUCUS AFTER IMMEDIATE HYDROLYSIS; ON HYDROLYSIS AFTER
STANDING 24 HOURS; AND ON HYDROLYSIS AFTER STANDING 24 HOURS
WITH ADDITION OF SPERMATOZOA

	PREOVULATORY PHASE OF CYCLE		OVULATORY PHASE OF CYCLE		POSTOVULATORY PHASE OF CYCLE		
	MG. % SUGAR	NO. OF SPECI-MENS	MG. % SUGAR	NO. OF SPECI-MENS	MG. % SUGAR	NO. OF SPECI-MENS	AVERAGE PER CENT
Immediate hydrolysis	0.819	64	0.391	61	1.103	138	
Hydrolysis after 24 hours	0.773	53	0.311	53	0.992	117	
Hydrolysis after 24 hours with addition of spermatozoa	0.655	18	0.249	14	0.932	43	
Decrements in per cent.—							
Hydrolysis after 24 hours	5.62		20.4		10.1		12.04
Hydrolysis after 24 hours with addition of spermatozoa	20.00		36.3		15.5		23.93

The essence of this communication is that the addition of washed sperma-
tozoa to cervical mucus results in a much greater sugar reduction in that medium
than occurs "spontaneously." This decrement, in both instances, moreover, is
particularly marked in material collected during the ovulatory phase when the
secretion is abundant and of low viscosity and cellularity, and when one might
presume that nature provides the optimal set of circumstances favorable to
fertilization. The general average decrease in the total amount of reducing

substances in cervical mucus alone on standing twenty-four hours was found to be 12 per cent. When washed spermatozoa were added to mucus and the analytical procedures carried out along the same lines, this reduction in sugar was augmented twofold, i.e., to the extent of 24 per cent. More light must be brought to bear on this subject before the authors can finally commit themselves on the cause of this decrement. In the meanwhile, they again affirm their belief that this sugar loss is referable to enzyme action. The part which bacteria may play in the speculation is not covered by this report. However, the addition of the washed spermatozoa enhances this catabolic process to a marked degree. One may be permitted the conjecture that the concept of continuity of the germ plasm may receive a new connotation—that spermatozoa on leaving the seminal fluid and on entering the uterine tract continue to live in an environment well adapted for their specific physiology.

Summary

Cervical mucus contains reducing substance, expressed as sugar, in amounts comparable to that reported for semen. On standing at room temperature for twenty-four hours the amount of sugar is reduced by some 12 per cent. When washed spermatozoa are added to the mucus in the amount of 1 million per 100 mg., the effected decrement in sugar, on standing twenty-four hours is doubled, and amounts to some 24 per cent. It is suggested that this destruction of sugar is due to enzyme action and that it serves a useful purpose in sperm metabolism.

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GLYCOGEN AND REDUCING SUBSTANCES IN VAGINAL MUCUS

Gestational and Cyclical Variations

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PREVIOUS work has indicated that there are wide fluctuations in the amounts of reducing substances in the tissues and secretions of the female genital tract during various phases of the menstrual cycle and pregnancy, particularly in the endometrium and the vagina, the ovaries, tubes, and cervix taking part to a lesser degree. These changes appear to be related to the physiological preparation for the transport of spermatozoa and nidation of the ovum, for which the glucose-glycogen system furnishes nutrition. Glycogen is present in the cumulus oöphorus, the Fallopian tubes, the endometrium, and the cervical and vaginal mucosa.

Laqueur[1] studied the glycogen content of the uterine endometrium in 48 regularly menstruating women and found that, in the proliferative phase, the glycogen value averaged 0.27 per cent, while during the secretory phase it averaged 0.86 per cent. These variations corresponded to the morphological differences in histologic preparations.

Zondek and Hestrin[2] recently summarized the present knowledge of the glycogen metabolism in the endometrium and emphasized the marked glycogen deposition during the progestational phase. The increased deposition of glycogen can be accounted for by increased phosphorylase activity.

A careful quantitative chemical study of the total fermentable and free reducing substances in cervical mucus was made by Viergiver and Pommerenke.[3] They found that the values were highest in the postovulatory phase, lower in the preovulatory phase, and lowest in the ovulatory phase. Reducing substances were always present, however, in amounts sufficient for spermatozoal survival.

According to Hughes,[4] the glycogenetic enzyme concentration in the human endometrium increases gradually from the beginning to the end of the menstrual cycle and corresponds to the histological findings of glycogen content as revealed by Best's carmine stain. Far greater concentrations of glycogen were found in biopsy material and curettings in early pregnancy. This latter finding has long been generally known and is correlated with the early nutritional needs of the ovum.

Even the vaginal mucosa takes part in these variations, and Smith[5] described these changes in detail. The histologic mucosal changes were characteristic in pregnancy, showing marked vacuolization of the cells of the basal zone.

In a recent study, Milton and Wiesner[6] applied swabs to the cervical canal. These were then dropped into alkaline copper sulfate for determinations of free reducing substance. With this qualitative method they found that most of their specimens in the ovulatory phase were positive, in the luteal phase negative, and in early pregnancy negative for reducing substances. These findings are not in agreement with those of the previously mentioned authors,[3, 4] a difference which might be explained on the basis of their respective methods.

The authors undertook the present study to determine whether the amounts of glycogen in vaginal mucus can be correlated with pregnancy. It was thought possible that the marked increase of intracellular glycogen in the endometrium and vaginal mucosa might be reflected in the mucus present in the cervix and vagina, especially since the superficial cells of the vagina and endometrium are constantly being desquamated.

Methods

Specimens of mucus were aspirated, with a glass pipette and rubber bulb, from the vaginal vault and collected in previously weighed test tubes. As much as possible was collected and divided into two approximately equal portions in separate test tubes. These were refrigerated immediately, weighed within a few hours, and kept under refrigeration until the chemical determinations were performed. Total weights of both specimens ranged from 50 to 950 mg. Specimens which were grossly bloody or purulent were rejected. Patients in various phases of the menstrual cycle, during early and late pregnancy, and six weeks post partum were used in the study.

The chemical procedures for reducing substances and glycogen were carried out essentially as by Viergiver and Pommerenke.[3]

Free Reducing Substance.—A weighed amount of mucus was suspended in 2 ml. water and stirred at intervals for one hour. The tube was then centrifuged and the supernatant analyzed for reducing substances by the Folin-Malmros[7] ferricyanide procedure.

Glycogen.—A weighed amount of cervical mucus was digested with 1 ml. of 30 per cent potassium hydroxide for one hour in a boiling water bath, to which was then added 3 ml. of 95 per cent alcohol. The tubes were allowed to stand overnight in the refrigerator, and then centrifuged. To the sediment were added 2 ml. of 1N sulfuric acid, heated for two hours in a water bath, neutralized, and an aliquot analyzed for reducing substance by the ferricyanide procedure.

All results were computed in grams per 100 grams mucus (wet weight).

Twenty-three patients were studied, of whom thirteen were pregnant. We will refer to the free reducing substances as glucose, although they were not established to consist entirely of glucose. Glucose and glycogen figures were used to calculate the ratio of glucose to glycogen. The total amount of glycogen in the entire specimen removed was also calculated.

Results

The average for glucose in pregnancy was 0.78 grams per cent, with a range of 0.26 to 2.03, while in nonpregnant subjects the average was 0.62 grams per cent with a range of 0.05 to 1.30. Glycogen levels in pregnant women averaged 2.1 grams per cent with a range of 0.25 to 4.92, and in nonpregnant women the average glycogen was 1.5 grams per cent with a range of 0.15 to 4.05. The ratio of glycogen to glucose averaged 4.2 in pregnancy, and 2.8 in nonpregnant patients. The total vaginal glycogen in pregnancy averaged 4.7 mg. with a range of 0.6 to 11.7, while in nonpregnant women the average was 2.6 with a range of 0.5 to 6.9. The values for glucose and glycogen in postmenstrual specimens were consistently lower than those taken during the secretory phase, as were samples taken six weeks post partum. The results are summarized in Table I.

TABLE I

	PREGNANT			NONPREGNANT		
		S.D.			S.D.	
Glucose	0.78 ± 0.31	0.44		0.62 ± 0.29	0.35	
Glycogen	2.01 ± 1.27	1.48		1.51 ± 1.44	1.65	
Ratio (glycogen/ glucose	4.2 ± 3.8	5.2		2.9 ± 2.3	3.1	
Total glycogen	4.7 ± 3.3	4.0		2.6 ± 1.9	2.3	

$$S.D. = \sqrt{\frac{\Sigma\,d^2}{n-1}}\ \text{where}$$

S.D. = standard deviation
d = average deviation
n = number of determinations

Discussion

The results reported here indicate that there is an apparent increase in the content of reducing substances, particularly glucose and glycogen, in the vagina as the menstrual cycle goes into its progestational phase and this increase continues into pregnancy. The postpartum levels are lower than those in the progestational phase.

The levels of glycogen and glucose as well as the ratio of glycogen to glucose were generally higher in pregnant when compared to nonpregnant subjects, with some overlapping in the range of both groups.

As a first approximation, the total glycogen in these specimens was estimated, assuming that the maximum amount of mucus possible was aspirated from each patient. The figures thus obtained showed the greatest difference between the pregnant and nonpregnant subjects.

It seems that ovulation and especially pregnancy are the stimuli for glucose and glycogen utilization, while early in the menstrual cycle and during the postpartum phase there is a lessened physiological need for these in the genital tract.

Because the histologic changes in early pregnancy are so marked,[4, 5] it is conceivable that improvement in this present technique will permit more distinct chemical differentiation of the pregnant and nonpregnant states than is apparent in the wide ranges which have been found up until now.

Conclusions

1. The reducing substances, particularly glucose and glycogen, in human vaginal mucus are increased during pregnancy. The total glycogen content shows the most distinct change.

2. The levels of glucose and glycogen are lowest during the postpartum and proliferative phases.

3. These variations parallel known histologic observations. Further improvements in technique may make these differences more obvious.

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A NEW ROTATING FORCEPS FOR OCCIPUT POSTERIOR AND OCCIPUT TRANSVERSE POSITIONS

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T O ENABLE proper evaluation of a new forceps, herewith presented, for the treatment of occiput posterior and occiput transverse, a brief résumé of the modern concept of these positions is indicated. Both of these positions will be considered together; indeed, many believe that occiput transverse, the so-called deep transverse arrest, is frequently a stage in the attempted spontaneous anterior rotation of a persistent occipitoposterior. Based on frequency and difficulties in management, these constitute one of the most important conditions in the practice of obstetrics. It is probably for this reason that the literature on this subject has become voluminous, the methods of treatment many, and the theories for its pathogenesis conflicting and confusing.

Pelvic morphology, per se, is not the primary factor in its causation. While Caldwell and Moloy have shown a high incidence in the android pelvis, Thoms pointed out an almost equally large number in the anthropoid pelvis. Indeed, with less frequency, it occurs in the gynecoid and platypelloid pelves as well. Regardless of the morphological type of pelvis, anterior rotation of the occiput is hindered or delayed by a narrowing of the midpelvis, resulting in prolonged and difficult labor. In a pelvis of ample capacity, anterior rotation is the most frequent phenomenon. However, an ever-increasing number of reports indicate that a fair number *do not rotate* anteriorly but remain in the posterior sacral position and are delivered (or may deliver spontaneously) as such.
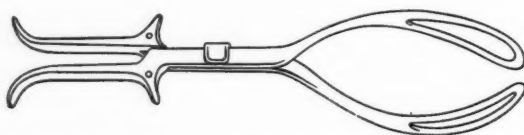

Fig. 1.

The operative measures advocated are many and each method enjoys a distinct vogue in different localities. Podalic version and breech extraction, manual rotation of the head, Kielland forceps, Barton forceps, Scanzoni maneuver, the key-in-lock maneuver and hands-off-midwife procrastination, each has its own advocates. However, none of these operative therapeutic methods simulate the normal mechanism of labor. In physiological labor, descent, flexion, and anterior rotation of the head occur simultaneously with each movement blending into the other. Anterior rotation begins in the midpelvis and is completed at the outlet, due to the resistance of the levator ani muscles. Anterior rotation (either manual or by instrument) is accomplished in *one plane*, at or above the level of impaction, through an arc of either 90 or 135 degrees, followed by downward traction with forceps; each part of the maneuver is separate and distinct. This tends to induce trauma to the fetal head as well as to the maternal soft parts.

In order to facilitate delivery of an occiput posterior in a manner more like that of normal labor, the author has devised and used the forceps described below and illustrated in Fig. 2. This forceps, like a Kielland forceps (Fig. 1) up to the indicator dots, similarly has no pelvic curve and has a sliding lock. The shanks are continued for 4 inches above the indicator dots, and end in grooves to receive the handle (Fig. 2, 2). This consists of ¾ inch hollow pipe of 9-inch length, mounted to a circular thrust ball bearing and fastened to

the grooved shanks by means of a wing nut. Therefore, this handle, when held in a horizontal position, enables the forceps to be rotated in any direction by the rotating bar (Fig. 2, 3).
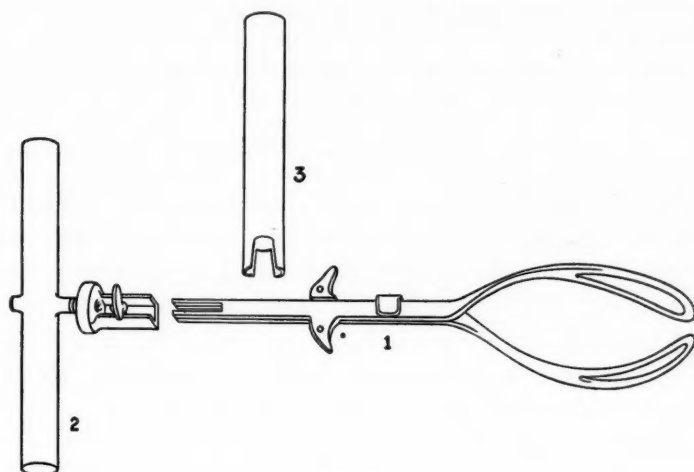
Fig. 2.
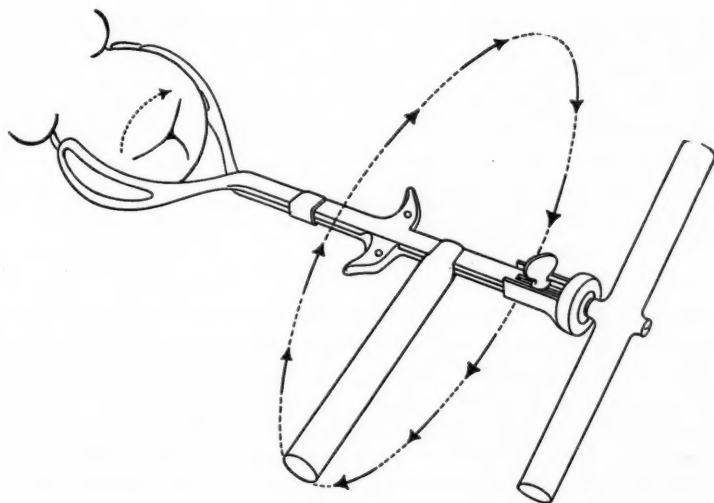
Fig. 3.

The technique of application is the same as that in Kielland forceps. The handle is attached to the shanks and gentle downward traction applied. Fig. 3 illustrates the forceps applied in right occipitotransverse position: the rotating bar is applied to the occiput side of the shanks, as indicated by the dots, and gentle clockwise rotation attempted, while synchronous downward traction is made. For left occipitotransverse, similar technique is followed but the rotation is counterclockwise. Rotation is accomplished, not in one plane, but in a helical curve. Frequently, rotation started by the bar continues spontaneously, due to the resistance of the levator ani muscles. This results in a greater dispersal of the forces over a larger area of the maternal soft parts, thereby decreasing the liability to severe trauma.

The author intends to report, in a subsequent article, the results obtained in a large group of cases.

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MARSUPIALIZATION FOR ADHERENT PELVIC MASSES

Report of Eight Cases

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MARSUPIALIZATION is not a new procedure. In 1876, Porro, in attempting to reduce the mortality from cesarean section, marsupialized the cervical stump. In 1924, Portes described a type of cesarean section, in badly infected cases, utilizing marsupialization of the uterus as a temporary procedure. Marsupialization has also been mentioned by Crossen[1] and by Berkeley in the treatment of irremovable cysts of the pelvis. Kelly and Noble,[2] and Berkeley and Bonney[3] advocate the procedure in the management of the adherent amniotic sac in abdominal pregnancy.

The marsupialization operation has been performed eight times during the past thirteen years on the Gynecological Service of the Mount Sinai Hospital. A variety of pathological conditions were encountered but all were predominantly inflamed or infected cysts of the ovaries. In each instance this approach was used only after all attempts at removal had been unsuccessful. The paucity of cases is understandable since pelvic masses that defy removal are rarely encountered. When complete extirpation is hazardous, endangering the adherent and adjacent viscera, the operation is indicated. The end results have justified the procedure.

Method

Marsupialization is performed as follows: The abdomen is opened through a suprapubic midline incision. The pelvic mass is emptied and as much as possible of the cyst wall is removed. The remaining adherent cyst walls are then sutured to the parietal peritoneum effecting marsupialization.

To prevent postoperative incisional herniation, the upper two-thirds of the parietal peritoneum is closed before the remaining peritoneum is sutured to the cyst walls. The upper two-thirds of the fascia is then closed. The rest of the fascia is sutured to the parietal peritoneum and cyst walls, completing the marsupialization.

Several iodoform, accordion, gauze packings are introduced into the cyst cavity. Rubber dams are placed above and below the sac in the peritoneal cavity if drainage is necessary. The skin is then closed around the packings and the drains.

The postoperative treatment of the wound consists of the gradual shortening of the packings until they are finally removed. The marsupial opening should be maintained until the cavity of the cyst is obliterated by shrinkage and granulation, a process requiring some weeks.

Case Reports

CASE 1.—G. P., a 31-year-old white woman, was admitted on Aug. 12, 1936, complaining of left lower quadrant pain. Her menses were regular and the last menstrual period had been July 28, 1936. In the lower abdomen a mass was palpated filling the left side and ex-

tending beyond the midline to the right. Laparotomy was performed the following day, revealing a uterus enlarged by fibroids to the size of an eight weeks' gestation. A grapefruit-sized endometrial cyst was intimately adherent to the left uterine wall, to the left pelvic wall, and to the transverse colon. The cyst was emptied and freed from the transverse colon. The uterus and right tube and ovary were removed, while the cervix and the endometrial cyst on the left were left. The surgeon felt that complete removal of the cyst was impossible because of adherence to the left pelvic wall and the large blood vessels. The cyst was therefore marsupialized, and several Penrose drains were placed in the cyst itself. A counter stab wound was made on the right side for drainage.

There was a low-grade fever for twenty days after operation accompanied by a thick mucopurulent discharge from the cyst. On the twenty-eighth day 10 per cent turpentine and mineral oil were injected into the sinus tract to help healing. The patient was discharged on Sept. 16, 1936, at which time the tract was found to be almost completely healed. On follow-up examinations Nov. 11, 1936, and May 26, 1937, the abdominal wound was found to be well healed, the sinus tract obliterated, and no pelvic masses palpable.

The patient was re-admitted on Sept. 14, 1948, because of lower abdominal distention of two years' duration and lower abdominal pain of six months' duration. A tender cystic mass had been found on follow-up examination on April 9, 1948, filling most of the pelvis. A barium enema outlined a large extrinsic mass in the pelvis. Examination in the hospital revealed that the cervical stump merged into a large cystic mass roughly the size of a five months' pregnancy. It filled the cul-de-sac and the right and left pelvis, and was adherent to the pelvic walls.

At operation on Sept. 20, 1948, the mass was found to be a large grapefruit-sized cervical fibroid. This was removed with some difficulty. There was no evidence of any sinus tract or any evidence of the endometrial cyst of the ovary which had been marsupialized in 1936. The patient did well and was discharged on Oct. 18, 1948, from her second operation, in good condition.

CASE 2.—A. E., a 42-year-old woman, was admitted on June 16, 1946, because of inability to void for twelve hours. She had had a hysterectomy twenty-six years before, for a tumor of the uterus. The entire pelvis and cul-de-sac were found to be filled with a hard movable cystic mass. At operation a large cantaloupe-sized mass was found firmly adherent to the sacrum, bladder, right lateral pelvic wall, and the soft structures laterally on the left side. Seven hundred cubic centimeters of clear, reddish-tinged fluid were aspirated. It was impossible to separate the cyst from the surrounding structures and the large blood vessels. After a biopsy was taken of the cyst wall, marsupialization was done, and the cyst was packed with accordion gauze. The pathological report was a tuboovarian cyst.

The postoperative course was good. Iodized oil was placed by catheter into the sinus tract, five weeks after the operation, revealing the presence of a small cavity. Sodium morrhuate (1 c.c.) was instilled into the sinus tract on three occasions in an attempt to obliterate the tract. This was partially successful and the patient was discharged on Aug. 13, 1946, on the forty-third postoperative day draining scant amounts of serous fluid. Examination eight months later showed the abdominal wound to be well healed, the cervix movable, and no masses in the pelvis.

CASE 3.—S. E., a 27-year-old woman, was admitted on Jan. 20, 1938, complaining of a growing mass in the lower abdomen. At 15 years of age she had had a bilateral salpingectomy and a unilateral oophorectomy. The menses were normal. An extremely tender abdominal cystic mass was felt reaching to two finger breadths above the umbilicus and filling the cul-de-sac. On opening the abdomen Jan. 20, 1938, free purulent fluid was found in the peritoneal cavity. A large perforated cystic mass occupied the right adnexal region and adhered to the small intestines and the sigmoid. The mass was mobilized as much as possible but complete removal was deemed injudicious because the bowel was firmly attached. The cyst was drawn out as far as possible and marsupialized. Two large accordion iodoform gauze drains were placed into the cyst cavity. The pathological report was a ruptured, infected, corpus luteum cyst.

The postoperative course was stormy. Subhepatic and subphrenic abscesses developed two weeks later and were drained by a right subcostal incision and drainage, with counter drains placed through a right lower quadrant incision. Three months later a posterior colpotomy was done for drainage of residual fluid in the ovarian cyst. The patient was discharged on the one hundred and sixth postoperative day. Follow-up examination, six months later, showed the abdominal and colpotomy wounds to be well healed, and no adnexal masses palpable.

CASE 4.—J. R., a 58-year-old woman, was admitted on Oct. 4, 1935, complaining of progressive enlargement of the abdomen, recent vomiting, and anorexia. The menopause was in 1931. Examination showed an acutely ill woman with cyanosis of the lips and marked dyspnea. Pelvic examination revealed a cystic resistance which appeared to fill the entire lower abdomen. A diagnosis of ovarian neoplasm was made, and since an acute accident had occurred immediate operation was necessary. On the same day under local anesthesia the abdomen was opened and found to contain turbid brown fluid. Thirteen liters of this turbid fluid were evacuated from the cyst which had ruptured spontaneously. All anatomical landmarks were lost and removal of the cyst was considered impossible. The cyst was drained, tissue was taken for diagnosis, marsupialization was done, and two iodoform accordion gauze packings inserted. The pathological report was papillary cystadenocarcinoma of the ovary. The patient developed bronchopneumonia, became progressively worse, and died on the thirty-first postoperative day.

Postmortem examination disclosed bilateral cystadenocarcinoma of both ovaries with hydroureter and hydronephrosis on the right side, chronic retrocolic phlegmon, and terminal bronchopneumonia.

CASE 5.—C. V., a 29-year-old Negro woman, was admitted on Jan. 6, 1948, for vaginal bleeding, vomiting and abdominal pain. Pelvic examination revealed a large semicystic mass occupying the entire lower abdomen. The diagnosis was a ruptured tuboovarian mass. At operation free pus was found in the peritoneal cavity, arising from an infected large tuboovarian cyst. An attempt to remove the uterus and the cyst was forestalled by the poor condition of the patient. Accordingly, the cyst was aspirated and marsupialized.

Though the immediate postoperative course was stormy, the patient subsequently did well and was discharged on the twenty-seventh postoperative day. The abdominal wound was well healed, and the tuboovarian mass was much smaller. Later examination revealed the pelvic mass to be considerably smaller.

CASE 6.—B. Y., a 28-year-old woman, was admitted on June 30, 1938, complaining of lower abdominal cramps of six months' duration. The menses were normal. Pelvic examination revealed a semicystic mass occupying the cul-de-sac. At operation the entire lower abdomen and pelvis were found to be filled with adherent loops of intestines. The uterus, tubes, and ovaries could not be defined, and no pelvic landmarks could be established. A thin-walled cyst was finally identified and ruptured during blunt dissection, spilling serosanguineous fluid. The greater part of the cyst was excised. Deeper in the pelvis, a boggy, fluctuant mass was palpated which on aspiration contained thick, greenish-yellow pus. The abscess cavity was evacuated and as much of the cyst wall as could be safely excised was removed. A large iodoform packing was introduced and brought out through the vagina, through a posterior colpotomy incision. The edges of the cyst were then sutured together over the packing, marsupializing the cyst through the vagina instead of through the abdominal wall. During the procedure, the bladder was accidentally opened. This was repaired in layers. The pathological report was a tuberculous ovarian abscess.

The patient was discharged on the thirty-third postoperative day. The abdomen was found to be well healed except for a small sinus. There was a tender cystic mass still present in the right lower quadrant.

The patient was re-admitted on Oct. 29, 1938, because of passage of urine from the abdominal incision. Her menses were regular, and there was no abdominal pain. The cervix was found to be in the axis of the vagina and the right adnexa were occupied by a mass the size of a small orange. Methylene blue was instilled into the bladder and appeared through

the abdominal sinus. The urine was negative for acid-fast organisms and cystoscopy revealed a small opening in the bladder. The vesicoabdominal fistula was excised on Nov. 5, 1938. The postoperative course was uneventful and the patient was discharged on Dec. 1, 1938 with no evidence of urinary leakage.

On follow-up examination on Feb. 24, 1942, the patient was found to be menstruating regularly. The pelvic mass was resolved to about the size of a peach. A ventral hernia was present but operation was not advised.

CASE 7.—P. S., a 33-year-old woman, was admitted to the hospital on April 28, 1947, complaining of a mass in the left lower quadrant. She had had intestinal operations for partial obstruction in 1931, 1934, and 1935, and an operation for a right ovarian cyst in 1942. The mass in the abdomen had become progressively larger and painful. Her menses were regular and her last menstrual period was April 17, 1947.

Examination revealed a large cystic mass occupying the left pelvis and the lower abdomen. A hysterogram revealed a large uterine cavity displaced to the right, and a barium enema showed the sigmoid and colon displaced to the right by a large extrinsic mass.

At operation on May 8, 1947, the peritoneum was found to be adherent to a large cystic mass which reached almost to the umbilicus. The lateral aspects of the cyst were adherent to the lateral parietal peritoneum. The cyst was aspirated, evacuating about 4,000 c.c. of fluid. The cyst was mobilized in its lower portion and the ovarian artery and vein ligated. A supravaginal hysterectomy was done. The cyst and uterus were gradually removed from the abdomen by dissecting the posterior wall of the cyst from the retroperitoneal structures. When three-fourths of the cyst were finally enucleated it was found that the dome of the upper fourth was covered by adherent small bowel. Complete removal was considered dangerous. Therefore as much as possible of the cyst was excised and the adherent portion was marsupialized and packed with iodoform gauze. The pathological report was a serous cyst of the ovary.

The patient, with penicillin therapy, had a smooth, uneventful, postoperative course. On discharge on June 9, 1947, on the thirty-second postoperative day, examination revealed a small sinus at the site of the marsupialization. The cervical stump was well healed and there were no pelvic masses.

Follow-up examinations on July 11, 1947, and on April 11, 1949, showed a well-healed abdominal scar and a negative pelvis.

CASE 8.—R. G., a 48-year-old woman, was admitted on Oct. 10, 1934, complaining of severe lower abdominal pain of five days' duration. Her menopause had occurred a year and a half previously. Examination revealed rebound tenderness in the entire abdomen with moderate distention. The uterus was normal and anteflexed. On the left, the lower pole of a mass could be felt but the exact extent of the mass could not be determined. Nineteen days after admission a posterior colpotomy was performed because of marked fluctuation in the cul-de-sac. A large amount of grayish material was obtained which was sterile on culture.

Because of the persistence of the abdominal pelvic mass, in spite of colpotomy and abdominal paracentesis, a laparotomy was done on Feb. 21, 1935. The surgeon felt that he had entered the cyst rather than the peritoneal cavity. About 3,000 c.c. of brownish fluid were evacuated mixed with sebaceous material and hair. The intestines were not visualized, nor could the cyst wall be freed from the adherent parietal peritoneum. The cyst reached from the cul-de-sac to the diaphragm. Since it was impossible to remove the cyst, it was marsupialized and iodoform packings inserted.

The patient did well. On two occasions the sinus tract was injected with Hippuran to determine the location and extent of the remaining cavity. A 4-inch oval cavity was demonstrated just above the bladder and a 6-inch sinus tract was noted extending to the abdominal wound. Repeated injections of pure 10 per cent turpentine in sterile Albolene were utilized in an attempt to sclerose and obliterate the cavity, but this was unsuccessful. The patient was discharged one hundred five days after the marsupialization with the advice to return for subsequent surgery.

When the patient was re-admitted four months later, the abdominal sinus was still present. She had gained 30 pounds and looked very much stronger. A cystic mass reaching almost to the umbilicus was felt on the left side of the abdomen. Injection of the sinus failed to reveal any cyst cavity. However, a 3½-inch sinus dipping into the pelvis was visualized.

The abdomen was opened on Nov. 4, 1935. The peritoneal cavity was practically obliterated by intimately adherent loops of large and small bowel. The adhesions were finally freed and the dermoid cyst arising from the left ovary was removed along with the sinus tract.

The patient's postoperative course was entirely uneventful. On discharge, Dec. 9, 1935, thirty-five days later, the wound was healing satisfactorily. The pathological report was a dermoid cyst with chronic and acute inflammation.

Examinations on March 11, 1936, and on Sept. 9, 1936, showed a well-healed abdominal wound, a negative pelvis, and a postoperative ventral hernia. The hernia was repaired on Feb. 1, 1937.

Comment

It is interesting to note that the pelvic masses completely disappeared in six patients, while in the seventh the mass was definitely smaller.

In Case 1, subsequent operation for an unrelated condition twelve years later did not reveal any evidence of the marsupialized cyst or sinus tract.

Two patients developed postoperative ventral hernias which were subsequently repaired. These occurred only in the cases requiring two operations. Sclerosing agents were used in four cases to hasten obliteration of the sinus tract with questionable results.

There was one mortality in a case of ovarian carcinoma with metastasis.

The hospital stay was rather prolonged but, with the use of antibiotics and chemotherapy in the more recent cases, the convalescent period was considerably reduced.

In one case it was found judicious to marsupialize the cyst through the cul-de-sac.

Marsupialization can also be used advantageously in cases where the patient's condition is so precarious as to contraindicate a more prolonged and shocking procedure.

In conclusion, the authors present eight cases where marsupialization of pelvic cysts was used successfully. Though the operation is practically forgotten, indications do arise for its usefulness, and should be borne in mind in those rare instances where it is impossible to remove completely an adherent cyst. In these cases it substitutes a simple procedure for one which may be more hazardous for the patient.

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1100 PARK AVENUE.
45 EAST 85TH STREET.

PENTOTHAL SODIUM, TERMINAL OBSTETRICAL ANESTHESIA

K. B. Boyd, M.D., and A. R. Jones, M.D., Baltimore, Md.

(From the Department of Obstetrics, Maryland General Hospital)

THE purpose of this paper is to help eliminate a certain fear which we feel exists in the minds of many obstetricians in regard to the use of Pentothal Sodium. In our minds, we were doubtful, too, but because of personal experience in the use of Pentothal Sodium in minor battle casualties during the last war, we felt that its trial in obstetrical deliveries was justified.

The largest series of cases (1,415) was reported in 1944 by Hellman and associates.[1] Previous to this time, others (LaBrecque,[3] Rucker[10]) and since this time still others (Mazzola,[5] Dippel[7]) have reported smaller series of cases. Their results were favorable and justify the continued use of Pentothal Sodium. However, its employment is not as widespread as it might be. It is not the purpose of this paper to review the literature exhaustively, but merely to add to it our experiences with a series of 294 cases since October, 1946. The results with our technique, we feel, have been excellent both for mother and child and indicate to us that Pentothal Sodium properly used has a place in obstetrical anesthesia.

Technique

Regardless of parity, all of our patients are carried through the first stage of labor with Seconal, Demerol and scopolamine analgesia. Seconal in 3 grain dosage is usually given with the patient in active labor and with about 3 cm. of cervical dilatation. If labor progresses uneventfully and the presenting part descends according to expectations, Demerol, 100 mg., with scopolamine, 1/150 grain, is given intramuscularly with a cervical dilatation of 6 to 8 cm., depending on the severity of the pains. With adequate sedation, the amount of Pentothal Sodium necessary for the actual delivery is less than if the patient is not properly sedated. The patient also takes the anesthesia more smoothly and the anesthesia level desired is more rapidly reached. This is in agreement with Hellman,[1] Helman, and Dippel.[7]

When the cervix is fully dilated and the patient is ready for delivery, vertex at or just above the perineum, she is placed on the delivery table, prepared, draped, and catheterized. A careful examination is made to determine rupture of the membranes, cervical dilatation, and position of the head. Everything being favorable, the administration of Pentothal Sodium is begun.

Pentothal Sodium 1 Gm., is dissolved in 40 c.c. of sterile distilled water making a 2.5 per cent solution. Previously prepared sterile sets, including a 20 c.c. syringe, two-way stopcock, rubber tubing, adapter, 1 oz. medicine glass, and No. 20 gauge needles, are available at all times. Twenty c.c. of the well-mixed and thoroughly dissolved Pentothal are placed in the syringe and the needle placed in an antecubital vein. Ten c.c., or 0.25 Gm., of Pentothal are slowly injected over a period of thirty to sixty seconds. Ordinarily, this produces within this length of time sufficient anesthesia to allow episiotomy and

outlet forceps delivery to be accomplished. If necessary, additional Pentothal up to 10 c.c. or 0.25 Gm. is given. Oxygen inhalation to the mother is begun as soon as she is anesthetized as a possible safeguard against fetal anoxia. Immediately following delivery, the cord is clamped and the infant removed to the resuscitator where suction of nose, nasopharynx, and pharynx is done. No effort is made to hasten the delivery of the placenta. Additional small amounts of Pentothal are administered as necessary for repair of the episiotomy. The average total amount of the drug necessary for completion should never exceed 1 Gm. In our series, the average amount was 0.717 Gm. Undue haste is not necessary to accomplish delivery of the baby. Hellman and co-workers[1] have shown that Pentothal Sodium passes through the placenta and within ten to twelve minutes the concentration of the drug in the mother and fetus are equal. There is a five-minute interval in which time the amount of drug reaching the fetus is very small. In our series of 294 cases, the average time from start of administration to the clamping of the cord was 3.8 minutes. The maximum time was seventeen minutes and minimum time was one minute. We feel from clinical experience that there is a safe time interval of eight minutes before anoxia of any severe degree is manifested in the baby.

TABLE I. SUMMARY OF 294 CASES

	CESAREAN SECTION	FORCEPS	EPISIOTOMY	SPONTANEOUS	BREECH
Primiparas	8	164	167	9	1
Multiparas	10	72	78	30	
Total	18	236	245	39	1

TABLE II. OPERATIVE DELIVERIES

POSTERIOR POSITIONS DELIVERED AS SUCH	OUTLET FORCEPS	SCANZONI	MIDFORCEPS	SECTION
6	222	6	2	18

Effect on the Mother

There is no doubt that from the viewpoint of the patient, Pentothal Sodium is one of the most pleasant of anesthetics. Induction is smooth and rapid with no worrysome stage of excitement. Relaxation produced is quite sufficient. Kassabohm and Schreiber[4] state that uterine contractibility and contractions are not impaired by this drug. In this series, no observations on uterine contractions were made. The postanesthetic period is also pleasant. There is usually absence of nausea and vomiting such as is seen with inhalation anesthetics. The patient, ordinarily, after a twelve-hour recovery period, is perfectly capable of eating a regular diet. There is absence of postoperative troublesome headache and occasional bladder incompetence as seen with saddle block anesthesia.

TABLE III. EFFECT OF ANESTHESIA ON MOTHER

GRADE I	GRADE II	GRADE III	GRADE IV
290	2	2	0

In our series of 294 cases, an attempt was made to grade the effect on the patient of Pentothal Sodium. Grade I was used to include those patients in whom induction was smooth and there were no postanesthetic difficulties

at all. Grade II included those patients in whom the period of induction was not smooth and slight difficulty was encountered. Grade III included patients in whom difficulties of a serious nature were present. Grade IV included anesthetic deaths.

There were no deaths in this series due either to the anesthesia or to other causes. Two hundred ninety mothers took the anesthesia well and had an uneventful recovery. Two mothers were classified as Grade II. One of these vomited after receiving 0.1 Gm. of Pentothal Sodium and the anesthesia was discontinued. No tracheal aspiration occurred and her postpartum course was uneventful. Why vomiting should have occurred is difficult to say, unless there was extreme sensitivity to the drug on the part of this patient. The other patient developed laryngospasm which was rapidly controlled by the insertion of an airway and the administration of oxygen. Laryngospasm is, perhaps, one of the most common complications of this anesthetic. This was the first time we had seen it happen and since then it has not recurred.

Two cases were classified as Grade III. The first patient vomited at the start of the anesthetic and respirations ceased. This occurred after administration of 0.3 Gm. of Pentothal Sodium. Tracheal aspirations and artificial respiration established regular breathing in eight minutes. No postoperative difficulties were manifested by this patient. The other patient suffered an immediate postpartum hemorrhage and became apneic; whether this was due to the blood loss or to the Pentothal Sodium is difficult to say, but more than likely it was caused by the hemorrhage. Postpartum hemorrhage occurred in one other case. We do not feel that the use of Pentothal Sodium and the occurrence of increased bleeding are related; otherwise, hemorrhage would have occurred more frequently and in the remaining 292 cases, no increase in blood loss was noted. In the literature, it is the consensus that there is no increase of blood loss with Pentothal.

In the group of 290 cases classified as Grade I, several obstetrical complications were present. Those patients who were sectioned for various reasons presented no difficulties. There were five pre-eclamptic mothers and one chronic nephritic mother, all of whom took the anesthetic well and developed no postanesthetic complications. One mother had Grade III cardiac disease on the basis of a rheumatic heart. One other was a diabetic. Both of these responded well to Pentothal Sodium. It is pointed out in the literature that Pentothal Sodium is excreted through the liver and that perhaps in those cases in which liver damage may be present, i.e., pre-eclampsia, care and thought should be taken before selecting Pentothal Sodium as the anesthetic agent. It is established that Pentothal does not influence the blood sugar.

Effect on the Infant

In this series of 294 cases, there were no fetal deaths. One infant was stillborn but this infant was known to be dead before delivery. The mother of this infant, it is interesting to note, is the one who stopped breathing only to regain respirations in eight minutes as previously described. Hellman reports no increase in fetal mortality over that with other types of anesthetics. LaBrecque,[3] in 80 cases, had no deaths but three infants required resuscitation. Mazzola,[5] in 50 cases, had no fetal deaths but seven drowsy infants. Dippel and associates,[7] in 35 cases, report ten fetal deaths but in none of these could the death be considered due to the anesthesia. However, 12.5 per cent of infants required little resuscitation and in 10.5 per cent, minor resuscitation was of no avail.

Nineteen infants out of 295 (there was one set of twins) did not cry spontaneously after delivery and required varying degrees of resuscitation.

Once again, as in the mother, an attempt was made to grade the effect of the anesthetic agent on the fetus depending on the degree of asphyxia: Grade I, infant died spontaneously; Grade II, mild degree of asphyxia with rapid response; Grade III, moderate to severe asphyxia but infant responded; Grade IV, death due to Pentothal.

TABLE IV. EFFECT OF PENTOTHAL ON INFANT

GRADE I	GRADE II	GRADE III	GRADE IV
276	18	1	0

Table V represents a summary of the 19 infants who required some degree of resuscitation. An attempt is made in the comment column to set forth essential points briefly and is self-explanatory to the reader.

TABLE V. SUMMARY OF INFANT ASPHYXIA

DELIVERY TIME (MINUTES)	DEGREE OF ASPHYXIA	SEDATION AND TIME BEFORE DELIVERY	RESUSCITATION	COMMENT
2½	II	Seconal 5' Demerol 4½'	Mask O$_2$ Aspiration	Cause—Pentothal?
5	II	Demerol 1'	Mask O$_2$	Demerol and traumatic delivery. Posterior delivered as such
5	II	Seconal 2', 15" Demerol 1' 30"	Mask O$_2$	Pentothal? Probably Demerol
4 7½	A-I B-II	Unknown	Mask O$_2$, twin B	Pentothal and prematurity
6	II	Demerol 1'	Mask O$_2$	Demerol and Pentothal?
4½	II	Seconal 7' Demerol 4' and 1'	Mask O$_2$	Pentothal ⅓ Gm. used. Cause—Demerol
Unknown	II	None	Mask O$_2$	Section. Pentothal?
5	II	None	Mask O$_2$	Section
6½	II	Seconal 4' Demerol 3' 40"	Mask O$_2$	Pentothal? 0.5 Gm. used
2	II	Seconal 4' Demerol 3' 10"	Mask O$_2$	Pentothal?
6	II	None	Mask O$_2$	Transverse, forceps rotation. Pentothal?
4	II	Demerol 4'	Mask O$_2$	Pentothal 0.38 Gm. used. Cause?
9	II	Seconal 1' Demerol 4'	Mask O$_2$	G.O.E. because of poor response. Cause—Pentothal
3	II	Seconal 2' 10" Demerol 1' 30"	Mask O$_2$	Pentothal 0.5 Gm. Cause—Demerol
8	II	None	Aspiration	First section. Ether also used. Cause—obstruction trachea
7	II	Seconal 14' Demerol 6'	Mask O$_2$	Pentothal?
17	III	None	Continuous O$_2$ aspiration Coramine	Third section. Cause—Pentothal
8	II	None	Mask O$_2$	Section. Cause?
3	II	Seconal 4' 25" Demerol 2' 55"	Aspiration	Pentothal 0.4 Gm. used. Cause—tracheal obstruction

In Table V, many question marks appear after the cause where Pentothal is given as such. In these cases, the infant did not cry spontaneously, some were sleepy, more likely from the Demerol given too late in the first stage of labor or due to obstruction of the airways by mucus. This, of course, will occur with all types of anesthesia and we feel that Pentothal Sodium in the majority of these cases cannot be cited as the causative agent.

Our greatest difficulty with the infants occurred in those patients who were sectioned. There were eighteen cesarean sections done; five of the infants delivered did not cry spontaneously. Although Pentothal is an ideal agent for sections, it does require that the operator be swift and skillful. Many authors state that Pentothal is ideal; however, many of these use local anesthesia to incise the skin before Pentothal is started. There is no doubt that in the experienced hand Pentothal works well but, in our opinion, Pentothal should not be used for sections by those of us who are inexperienced with it and are relatively slow and deliberate operators.

Included in these 295 infants were four premature infants. All except the second of twins cried spontaneously. It is not our general policy to use Pentothal Sodium in cases where a premature infant is expected, in multiple pregnancy, in breech deliveries, or in any other type of delivery during which any sort of difficulty is anticipated.

Summary and Conclusions

The purpose of this paper is to record 294 cases in which Pentothal Sodium was used for obstetrical deliveries and, by this addition, help to allay certain fears existing concerning the use of Pentothal Sodium.

The technique is described. To this it should be added that all of our anesthetics are given by house officers who have gained a fair amount of experience with the use of Pentothal. It is recommended that the promiscuous use of Pentothal by untrained personnel be avoided.

We believe that Pentothal Sodium is a valuable adjunct to obstetrical anesthesia. Its use, however, must be supervised and most certainly, it can be used with safety only in selected cases. It is by no means the only anesthetic agent for all deliveries.

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Department of Reviews and Abstracts

Selected Abstracts

Gynecologic Operations

Louros, N. C.: Principles of Myomectomy, Gynéc. et obst. **48:** 262, 1949.

The author summarizes his experience with myomectomy at the University of Athens from 1932 to 1948. He performed 400 myomectomies, 36 of them on pregnant women. The over-all mortality was 4.25 per cent; this was reduced to 1 per cent in the last 100 patients of the series. The mortality in 52 patients whose endometrial cavity was invaded was 9.61 per cent, as compared with 3.2 per cent in 312 operations with intact mucosa. The mortality among the 36 pregnant patients was 5.55 per cent. Miniature cesarean section was performed on 20 of these women; 5 aborted spontaneously; and 11 went to term. The author routinely performs myomectomy for fibroids discovered in women under 45. No attention is paid to size, number, or location of the tumors. The cervix is carefully examined preoperatively, with biopsy in any doubtful case. Patients having vaginal bleeding receive dilatation and curettage ten days prior to myomectomy.

The author prefers a single uterine incision, or at most two. All myomatous nodules are extirpated before any reparative suture is placed. Ligature is reserved for definite bleeding points; oozing is controlled by obliteration of all dead space in the operative defect by means of an inverting suture. The uterus returns to normal shape and full biologic function within three months.

DOUGLAS M. HAYNES.

Gynecology

Funck-Brentano, P.: Primary Lipoma of the Broad Ligament, Gynéc. et obst. **48:** 287, 1949.

The author points out that primary lipomas are commonly encountered benign retroperitoneal tumors, but they occur only with extreme rarity between the folds of the broad ligament. Only twenty reports of primary lipoma of the broad ligament could be collected from the world literature, and the author adds a twenty-first. The symptomatology caused by these tumors is either minimal or dependent on mechanical pressure effects. The tumors must attain considerable size before giving rise to clinical manifestations, and signs of venous compression have been noted only when the tumor is of enormous proportions. Pure lipomas are usually benign, and the incidence of malignant transformation of fibrolipomas would appear to be less than is the case in similar retroperitoneal tumors. Incomplete extirpation is often followed by local recurrence. The treatment is exclusively surgical.

DOUGLAS M. HAYNES.

Malignancies

McKelvey, John: Treatment of Carcinoma of the Vulva (Editorial), Surg., Gynec. & Obst. **89:** 242, 1949.

The author emphasizes that carcinoma of the vulva is not a clinical entity but includes carcinoma of the clitoris, of Bartholin glands, and occasionally melanosarcoma of

the vulva. However, inasmuch as the vast majority of these tumors are common epithelioma of the labia or adjacent perineal tissue, and inasmuch as the treatment is similar, the classification under one heading has not been detrimental.

He points out that there were astonishing variety and combinations of treatment at the University of Minnesota from 1928 to 1938. This variation in treatment yielded a five-year cure rate of only 15 per cent. No single stage of radical vulvectomy was done during this time, in spite of the fact that everyone who had studied the clinical material concluded that simple vulvectomy or irradiation were satisfactory treatments.

The reasons for the various unsatisfactory methods of treatment apparently arose from the fact that many of the patients were old and were poor surgical risks. There was a feeling, because of the poor results of minor surgery, this disease was incurable. Finally, too much importance was ascribed to the problem of primary healing. Ten years ago, the group at the University of Minnesota began to use single-stage radical vulvectomy performed under local procaine and Adrenalin anesthesia. More than 90 per cent of the patients seen were so treated. No serious aftereffects have been observed although occasional edema of one or both legs developed. More than 50 per cent of the patients were alive and free from tumor after five years. Six per cent of the patients operated on died before discharge from the hospital.

The author concludes that radical vulvectomy under local anesthesia, applied as early as possible but irrespective of the earliness or lateness of the local tumor and irrespective of the age and general physical status of the patient, offers an opportunity of reasonably safely increasing by three- to fivefold the salvage rate in this condition.

LOUIS M. HELLMAN.

Watson, James R., and Fetterman, George H.: Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast, Surg., Gynec. & Obst. **88:** 702, 1949.

The authors used testosterone propionate in the amount up to 3,900 mg. to treat seven patients with advanced carcinoma of the breast. In analyzing this small series of cases they were unable to find any evidence that testosterone propionate had any specific inhibitory effect on advanced carcinoma of the breast, that it altered the course of the disease, or that it resulted in any improvement over the survival rates obtained by the more commonly accepted forms of therapy. Systemic improvement did occur, however, and consisted of gain in weight and strength. This appeared after two to three weeks of treatment but was only temporary. In addition, pain from bone metastases was somewhat alleviated.

LOUIS M. HELLMAN.

Miscellaneous

Suzor, R., and Poli-Marchetti: Influence of Air Travel on the Female Genital System, With Particular Reference to Pregnancy, Gynéc. et Obst. (suppl.) **1:** 110, 1949.

The influence of air travel on the genital physiology of nonpregnant, lactating, and pregnant women was studied. Air hostesses whose specific duties kept them in the air much of the time observed an eight- to twenty-day lengthening of their menstrual cycles, associated with hypo- and oligomenorrhea. Several women in this group developed dysmenorrhea for the first time.

In a group of lactating women, lactation which had been normal during flight ceased approximately twenty-four hours after returning to the ground for average periods of forty-eight hours.

A group of twenty-six pregnant women at various periods of gestation was studied under conditions of air travel. Threatened abortion occurred fourteen times, spontaneous abortion twice, and premature labor, three times. Seven patients made the trip without incident. Fourteen women in the third trimester noted fainting tendencies and abdominal discomfort. Four women beyond the fifth month began bleeding vaginally after two hours of flight, and were delivered soon after landing at their destinations. One patient was

delivered of a premature stillborn infant of six and one-half months' gestation; she suffered a severe postpartum hemorrhage which was spontaneously controlled after she returned to the ground. The authors conclude from their observations that air travel is not the most advisable means of transportation for the pregnant woman.

DOUGLAS M. HAYNES.

Nemirovsky, Jose, and Martinez, Alberto Raul: Chiari-Frommel Syndrome, An. brasil. de ginec. **27:** 93, 1949.

The writers, from San Paulo, report a case of a 24-year-old woman, delivered two years before, exhibiting galactorrhea, neurovegetative disturbances, and a uterus sounding but 6.5 cm. The patient had been persistently amenorrheic for nearly three years.

The authors stress the rarity of the Chiari-Frommel Syndrome characterized by postpartum genital atrophy, amenorrhea, and persistent postweaning galactorrhea, and conclude that while the pathogenesis is still obscure, they believe it is due to the persisting function of the pituitary lactogenic hormone—prolactin, that inhibits pituitary gonadotropic activity.

C. E. FOLSOME.

Ribeiro, Flexa: Gynogram, An. brasil. de ginec. **27:** 99, 1949.

The author, Director of Fine Arts at the University of Brazil, coins the word ''Gynogram'' to define the study of methods of representing woman's form in art. He illustrates representations of the female figure through various ages from prehistoric times, when nature's greatest perfection appears deformed by artists' incapacities, until now, when it is again disfigured by modernists' extravagance. In the writer's opinion only the classical period, the peak of which was attained in Greece, might be considered genuine art. This unusual article on art, appearing in a gynecological journal, is well illustrated with twelve figures.

C. E. FOLSOME.

Mengert, William F.: Estimation of Pelvic Capacity, J. A. M. A. **138:** 169, 1948.

The author mentions five components of cephalopelvic disproportion: (1) size and shape of the bony pelvis, (2) size of the fetal head, (3) force exerted by the uterus, (4) moldability of the head, and (5) presentation and position. Only the first of these is susceptible to accurate measurements. Radiographic pelvic measurement is not feasible for all pregnant women. Moreover, it is unnecessary when manual methods indicate an obviously adequate pelvis. The author observed that the best index of either inlet or mid-plane capacity is the product of the transverse and the anteroposterior diameters. This necessitate radiographic measurements. The problem confronting the obstetrician is an accurate evaluation of these measurements. In general, inlet and mid-plane tended to vary together.

WILLIAM BERMAN.

Kueger, Vera I.: The Value of Albumin-Fortified Anti-Rh Serum for Rh Testing, M. J. Australia, p. 233, Feb. 19, 1949.

The author has shown that saline suspensions of red blood cells can be tested for the Rh factor by direct incubation with serum containing blocking antibodies, provided these are fortified by the addition of a suitable concentration of bovine albumin. Rh-positive cells show gross clumping after incubation for thirty minutes at 37° C. if only a small drop of cell suspension is used. This precaution is necessary and may be explained by Wiener's statement that slight dilution of plasma or serum with isotonic aqueous solution causes the dissociation of the albumin-globulin complex ''conglutinin'' into albumin and globulin. These in themselves have little or no conglutinating activity.

WILLIAM BERMAN.

Correspondence

Uterine Muscle Physiology

To the Editor:

In the article by Drs. Bickers and Woods entitled "Uterine Muscle Physiology from Laboratory to Bedside, A Treacherous Crossing" (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, December, 1949), bibliographic reference is made to a paper by Bickers and Main[1] relative to a method of recording uterine contractions in nonpregnant women, the influence of the pituitary-ovarian cycle on the pattern of uterine motility, and the loss of motility after bilateral oophorectomy. While the earlier publication does describe the technique of recording the contractions and the pattern of motility in more detail than the present article, the manner in which the references are made is misleading and does an injustice to the investigators who devised the technique[2] and made the original observations.[3]

LEO WILSON, M.D.

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NEW YORK, N. Y.
JAN. 12, 1950.

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Reply by Dr. Bickers

To the Editor:

Referring back to the original article published by Bickers and Main in the *Journal of Clinical Endocrinology* of January, 1941, it will be seen that reference is made to the original observations, which were confirmed by our study. The technique for recording uterine contractions has evolved slowly over the years and many have contributed to improvement in technique, among them Dr. Leo Wilson, himself. I did not feel that it was necessary in subsequent publications to refer back to the original contributors.

WILLIAM BICKERS, M.D.

RICHMOND, VA.
JAN. 31, 1950.

Treatment of Rh-Negative Pregnant Women

To the Editor:

The paper published in your January issue by Drs. Hoffman and Edwards entitled "A Preliminary Report on a New Concept in the Treatment of Rh-Negative Pregnant Women" begs comment. The suggestion that a progesterone derivative together with vitamin K might suppress Rh antibody formation is so novel, a critical examination of their data would seem warranted.

The authors apparently began their therapy with the impression contained in the statement: ''It is well known that Rh-negative women have a greater tendency during pregnancy to uterine contractility and to bleeding and early abortion.'' The authors do not differentiate between sensitized Rh negatives and nonsensitized Rh negatives. If an Rh negative is shown to be definitely not sensitized during a particular pregnancy, then erythroblastosis is very unlikely to occur in the offspring of that pregnancy. Usually if no Rh antibodies are found by repeated careful tests near term, then there is no reason to consider further the Rh Factor for that pregnancy.

The question of whether immunized (or ''sensitized'') Rh negatives show a higher miscarriage rate in the pregnancies prior to the occurrence of an immunized pregnancy, than nonimmunized Rh negatives or Rh positives, is still definitely controversial. One of the best discussions on this point is contained in a paper by Bentley Glass published in the February, 1949, issue of your JOURNAL. Dr. Glass made a careful statistical study of a large series of such patients and came to the conclusion that there was no significant difference in miscarriage rates among these three groups.

The erroneous notion that most if not all Rh-negative mothers bearing the offspring of an Rh-positive father will have infants affected with erythroblastosis is widely held and apparently subscribed to by Drs. Hoffman and Edwards. On the contrary, most of the incompatibilities never result in maternal sensitization and therefore clinical symptoms of erythroblastosis are seldom seen in these offspring. The figure usually quoted on this point is 5 per cent of Rh incompatibilities (Rh-negative mother with positive offspring) result in maternal immunization and possible (or probable) erythroblastosis in the offspring.

It is interesting that so few Rh negatives ever become sensitized. It may be that the Rh antigen is so weak that few individuals are sensitized by it. It is known from deliberate attempts to immunize Rh-negative males that many individuals are apparently refractory to the Rh antigen even after large quantities of Rh-positive whole blood are administered intravenously. Since pregnancy is a much less effective means of producing immunization than direct blood transfusion, it is not surprising that most of the Rh negatives never develop antibodies and therefore never have erythroblastotic offspring.

In addition, the incidence of erythroblastosis varies with the number of the pregnancy and it is careless to lump cases as ''multiparas.'' Furthermore, Drs. Hoffman and Edwards state: ''At the present time some of the infants delivered have not been typed.'' Since approximately 29 per cent of the offspring of all Rh negatives are Rh negative too and will not have symptoms of erythroblastosis whether their mothers were sensitized or not, this omission is unpardonable.

<div align="right">ROGER W. MARSTERS, PH.D.</div>

2065 ADELBERT ROAD
CLEVELAND, OHIO
JANUARY 27, 1950

Reply by Dr. Hoffman

To the Editor:

In view of the fact that this was a preliminary report only and until the complete bulk of our study is included in a further report, we feel that a rebuttal to Dr. Marsters' letter is entirely unnecessary.

<div align="right">PHILIP B. HOFFMAN, M.D.</div>

Intravenous Pitocin Infusions

To the Editor:

Within the past two years, four articles have appeared on the subject of intravenous Pitocin infusions for the induction or stimulation of labor. The first to appear was by Theobald and associates (British Medical Journal 2: 123, 1948), while the most recent two were in the January, 1950, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

It is interesting to note that each article begins with an historical background and that each has overlooked the fact that the use of intravenous infusions of dilute Pitocin was described in 1943 by E. W. Page (Proc. Soc. Exper. Biol. & Med. **52:** 195, 1943). Probably this was due to the fact that his report dealt primarily with Pitocin Tannate in Oil, but he wrote: "The most physiologic responses in severe primary uterine inertia have actually been obtained by giving an intravenous infusion of normal saline containing 10 or 20 units of Pitocin to the liter. By constant observation and controlling the number of drops per minute, the obstetrician may control the character and amplitude of contractions quite adequately. . . ."

As a result of Dr. Page's initial observations in 1941, the employment of Pitocin infusions for inertia, missed abortions, hydatid moles and certain inductions of labor has been a common practice in the San Francisco Bay area for almost a decade. In the last seven years, the concentration has been reduced usually to a 1:5,000 dilution in glucose and water, with an initial rate not exceeding 20 drops per minute. While we know of no untoward results in many scores of cases, a description of the accumulated experience still awaits the collection of many more cases before the possible dangers can be truly assayed. Certainly it seems inadvisable to utilize this technique to overcome cephalopelvic disproportion, as suggested by the British writers.

LEE D. FULTON, M.D.

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SAN FRANCISCO, CALIF.
FEBRUARY 14, 1950

Beta-glucuronidase Activity

To the Editor:

Because of current interest in the work on beta-glucuronidase activity, a statement summarizing our findings is presented. In respect to assays on blood serum, a three- to fourfold increase occurs during normal pregnancy. During toxemic pregnancy the results are not consistent; activity appears to be elevated in only two-thirds of patients with pre-eclampsia. Women with previous pre-eclampsia and previously high serum activity have been followed through subsequent normal pregnancies without an elevation in serum activity. Serum activity is not significantly altered in women with cancer. The original method described by Talahy and co-workers[1] seems best for serum assays.

In respect to assays on tissues and vaginal secretions the optimum pH for analysis varies from tissue to tissue. For practical purposes a pH of 4.5 may be used. The activity in malignant cervix, vagina, and vulva is higher than that in their benign counterparts. The reaction is most specific for cervix. The activity of malignant endometrium and ovary is not altered from the activity observed in benign tissues of these organs. The activity in vaginal secretions of patients with untreated cervical cancer, and most cases of corpus cancer, is above 300 units. Obviously, this is not a specific reaction since values over 300 units are observed in 20 per cent of women without cancer. Organisms isolated from the vagina and grown with menthol glucuronide will liberate enzyme activity. Irradiation (radium) will decrease activity in both vaginal secretions and in cervical tissues. The assay of vaginal secretions and tissues as a method of follow-up on cancer patients offers promise. The substrate (phenolphthalein glucuronide) may be obtained by writing us. Any teaching institution wishing 1 gram of substrate for clinical investigation may have it free of charge.

L. D. ODELL, M.D.
W. J. DIECKMANN, M.D.

CHICAGO LYING-IN HOSPITAL
5841 MARYLAND AVENUE
FEBRUARY 17, 1950

Reference

1. Talahy, P., Fishman, W. H., and Huggins, C.: J. Biol. Chem. **166:** 757-771 (1946).

Panhysterectomy for Uterine Carcinoma

To the Editor:

I believe there is general agreement that the essential treatment of adenocarcinoma of the endometrium in a woman presenting no contraindication to major surgery consists of complete removal of the uterus and attached adnexa. That such surgery rarely yields better than a 65 to 70 per cent incidence of five-year survivals suggests that a more extensive dissection would achieve better results. Even with so-called planned therapy utilizing both irradiation and surgery, the five-year survival rate can be improved.

Recently, we have been removing the regional nodes in addition to a wider resection of parametrium and vagina, similar to the Wertheim procedure employed for cervical carcinoma. In twenty cases, when the uterus was removed five to six months after intrauterine radium therapy (average dosage: 50 mg. for 120 hours) section of the iliac nodes revealed viable-looking adenocarcinoma in four patients, suggesting that perhaps 20 per cent of patients certainly were not curable by the ordinary type panhysterectomy. I would like to suggest that a more radical operation with removal of the regional iliac nodes may not be overtreatment of this disease.

The incidence of adenocarcinoma of the fundus is such that treatment of a significant series of cases requires many years if only an individual or single clinic is concerned. Perhaps through correspondence sufficient cases may be accumulated to permit evaluation of a more extensive resection than usually implied by a ''panhysterectomy'' for adenocarcinoma of the fundus. Letters to the JOURNAL or personal communications would certainly be appreciated.

CLYDE L. RANDALL, M.D.

BUFFALO GENERAL HOSPITAL,
BUFFALO, N. Y.
MARCH 4, 1950.

Items

Publication of Case Reports

In view of limitations of space in the JOURNAL, it was found necessary some years ago to decline the acceptance of reports of individual cases. However, with the recent expansion in the number of pages, we have decided, in response to a general demand, to include such reports in a separate department, in the July issue. These reports will be limited to cases of an unusual character, presented as briefly as possible, and without extended references to the literature, prolonged comments, or long bibliographic lists. An introductory paragraph outlining the purposes of the report can be included.

THE EDITORS.

American Board of Obstetrics and Gynecology

The American Board of Obstetrics and Gynecology announces that the following physicians will serve as Associate Examiners at the coming oral and pathology examinations to be held at The Shelburne in Atlantic City, N. J., from May 21 to 28, inclusive:

C. A. Behney, M.D., Los Alamos, N. Mex.
Leroy A. Calkins, M.D., Kansas City, Kan.
Samuel A. Cosgrove, M.D., Jersey City, N. J.
Russell R. deAlvarez, M.D., Portland 5, Ore.
Josiah R. Eisaman, M.D., Pittsburgh, Pa.
George H. Gardner, M.D., Chicago, Ill.
John W. Harris, M.D., Madison, Wis.
Andrew A. Marchetti, M.D., Washington, D. C.
John L. Parks, M.D., Washington, D. C.
Ralph A. Reis, M.D., Chicago, Ill.
Herbert E. Schmitz, M.D., Chicago, Ill.
Ward F. Seeley, M.D., Detroit, Mich.
Frank E. Whitacre, M.D., Memphis, Tenn.

PAUL TITUS, M.D., Secretary.

The International and Fourth American Congress on Obstetrics and Gynecology

The following addresses are to be given at the morning sessions of the International and Fourth American Congress on Obstetrics and Gynecology.

Dr. Arthur Hertig of the Harvard Medical School will speak on ''The Implantation of the Human Ovum.'' Discussion will be by Dr. Axel Westman of Stockholm, Sweden.

Professor Robert Courrier of the College of France in Paris will speak on ''Some Recent Observations on the Physiology of Reproduction.'' Discussion will be by Dr. Bernhard Zondek of Tel Aviv.

Dr. Samuel Reynolds of the Department of Embryology, Carnegie Institution in Baltimore, Md., will speak on "The Contractility of the Human Uterus and Its Physiological Basis." Discussion will be by Dr. José Botella-Llusia of Madrid.

Professor Carl Kaufmann of the University of Marburg, Germany, will speak on "Psychological Factors Affecting Ovarian Function." Discussion will be by Dr. Willard M. Allen of Washington University, St. Louis, Missouri.

Professor Hans Kottmeier of the Radiumhemmet in Stockholm, Sweden, will speak on "The Therapy of Gynecologic Cancer." Discussion will be by Dr. Norman F. Miller of the University of Michigan in Ann Arbor.

Dr. Herbert Traut of the University of California will speak on the "Early Diagnosis of Uterine Carcinoma." Discussion will be by Dr. Ragnevald Bredland of Oslo, Norway.

Professor Heinrich Martius of the University-Frauenklinik at Gottingen, Germany, will speak on "The Treatment of Cancer of the Cervix." Discussion will be by Mr. Charles Read of London.

Professor Leon Gerin-Lajoie of the University of Montreal will speak on "Uterosalpingography in the Differential Diagnosis of Uterine Bleeding." Discussion will be by Dr. Claude Beclere of Paris, France.

Professor Manuel Luis Perez of the University of Buenos Aires in Argentina will speak on the "Usefulness of Antibiotics in Obstetric Surgery." The discussant is not yet arranged for.

Dr. Carlos D. Guerrero of Mexico City will speak on "The Conservative Management of Myoma Uteri." Discussion will be by Dr. Julian Waldo Ross of Howard University at Washington, D. C.

Dr. Walter Seegers of Wayne University in Detroit, Mich., will speak on "The Nature of the Blood Coagulation Mechanisms and Its Relationship to Some Unsolved Problems in Obstetrics and Gynecology." Discussion will be by Dr. H. de Watteville of Geneva, Switzerland.

Professor Harold L. Sheehan of the University of Liverpool in England will speak on "The Kidney in Abruptio Placentae." Discussion will be by Dr. A. van B. Bastiaanse of Amsterdam, Holland.

Professor Lakamanaswami Mudaliar of the University of Madras in India will speak on an aspect of the pathologic physiology of pregnancy. The paper will be discussed by Dr. Manuel B. Rodriguez Lopez of Montevideo, Uraguay.

Professor Arnaldo de Moraes of the University of Brazil in Rio de Janeiro will speak on "Total Hysterectomy in Non-malignant Conditions—Indications and Techniques." The discussion will be by Dr. Tassilo Antoine of Vienna.

Professor Toshio Hasegawa of the University of Tokyo will speak on "Changing Incidence of Various Obstetrical and Gynecological Disorders During the War Years." Discussion will be by Dr. Erik Rydberg of Copenhagen.

Professor G. Dellepiane of the University of Turin has prepared a paper on the cytology of malignant cells. He will be aided in its presentation by Professor Claudio Braigozzi of Turin.

Dr. Birger Lundquist of Stockholm will speak on "Maternity Care in Sweden," and his paper will be discussed by Miss Ruth Taylor, R.N., of the Children's Bureau, Washington, D. C.

Dr. Marian Yang of Peking and Geneva will speak on "Maternity Care in China," and her paper will be discussed by Dr. Nicholson J. Eastman of the Johns Hopkins Hospital in Baltimore.

Dr. Dorothy Taylor, Senior Medical Officer for Maternity and Child Welfare of the British Ministry of Health in London, will speak on "The Evolution of the British Maternity Service," and her paper will be discussed by Dr. J. S. Collings, Research Fellow of the Nuffield Provincial Hospital Trust of London, England.

Dr. George Baehr, Chairman of the Board of Directors of the Health Insurance Plan of Greater New York will speak on "Maternity Care Under the Insurance Plan of Greater New York," and his paper will be discussed by Dr. Benjamin Watson, President of the New York Academy of Medicine.

Dr. Leonard Goodman, Director of the Maternity Hospital at Korle Bu, Accra in the Gold Coast Colony of West Africa, will speak on "Maternal Care in Africa." His paper will be discussed by Dr. Honoria Acosta-Sison of Manila, P. I.

All of the foregoing papers and discussions will be presented at general sessions of the Congress taking place in the ballroom of the Hotel Statler on Monday through Friday mornings, May 15 to 19, 1950.

American Association of Blood Banks Announces Site of Third Annual Meeting

The Third Annual Meeting of the American Association of Blood Banks is being planned for October 12, 13 and 14 at the Stevens Hotel in Chicago. The central location was chosen so that the meeting will be more accessible to members from all points of the country. The program which is being planned will be one which will attract blood bank personnel, hospital executives, pathologists, clinicians, surgeons, and other people interested in the procurement, preservation, and administration of blood and blood derivatives. For further information write the Office of the Secretary, 3301 Junius Street, Dallas 1, Texas.

Announcement

The Committee on Human Reproduction of the National Research Council will hold its annual two-day conference on some phase of reproduction at the Hotel Commodore, New York, on May 22-23, 1950. The subject for this year will be testis and ovary, eggs and sperm.

Among the speakers will be David W. Bishop, University of Massachusetts; L. C. Dunn, Herbert Elftman, and Earl T. Engle, Columbia University; Helen Deane, Harvard Medical School; Henry A. Lardy, University of Wisconsin; John McLeod, Cornell Medical College; Warren O. Nelson, University of Iowa; Jack Schultz, Cancer Research Institute, Philadelphia; and George D. Snell, Jackson Memorial Laboratory, Bar Harbor.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President*, Joseph Baer. *Secretary*, Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Annual meeting, May 11, 12, 13, 1950, The Greenbrier, White Sulphur Springs, Va.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President*, Samuel A. Cosgrove, Jersey City, N. J. *Secretary*, L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas. Annual meeting Hot Springs, Va., September 7, 8, 9, 1950.

Central Association of Obstetricians and Gynecologists. (1929) *President*, Lawrence M. Randall, Rochester, Minn. *Secretary-Treasurer*, John I. Brewer, 24 West Ohio St., Chicago 10, Ill. Annual meeting to be held Thursday, Friday, and Saturday, Sept. 21, 22, and 23, 1950, at the Hotel Schroeder, Milwaukee, Wis.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President*, Lester A. Wilson, Charleston, S. C. *Secretary-Treasurer*, John C. Burwell, Jr., 416 Jefferson Bldg., Greensboro, N. C. Annual meeting, Ormond Beach Hotel, Ormond Beach, Florida, Feb. 8, 9, and 10, 1951.

A. M. A. Section on Obstetrics and Gynecology. *Chairman*, James R. Blos, Huntington, W. Va. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June 19-26, 1950, San Francisco, Calif.

New York Obstetrical Society. (1863) *President*, R. Gordon Douglas. *Secretary*, Charles M. McLane, 33 East 68th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President*, Newlin F. Paxson. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President*, Eugene A. Edwards. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President*, William T. Daily. *Secretary*, J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President*, Houston S. Everett. *Secretary-Treasurer*, W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President*, Edward Friedman. *Secretary*, Robert R. Pierce, 116 William Howard Taft Road, Cincinnati 19, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President*, R. A. D. Gillis. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. Meetings, first Monday of each month, October to May.

Obstetrical Society of Boston. (1861) *President*, Roy J. Heffernan. *Secretary*, Francis Rouillard, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President*, Philip H. Arnot. *Secretary-Treasurer*, R. Glenn Craig, 490 Post St., San Francisco, Calif.

Washington Gynecological Society. (1933) *President*, George Nordlinger. *Secretary*, Stafford W. Hawken, 1150 Connecticut Ave., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Conrad G. Collins. *Secretary,* E. W. Nelson, 1407 S. Carrollton Ave., New Orleans, La. Meetings held October, November, January, March, and May.

St. Louis Gynecological Society. (1924) *President,* Matthew W. Weis. *Secretary,* Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo., Regular meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Donald Dallas. *Secretary,* Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* Julius McIver, Dallas. *Secretary,* George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* O. W. Picard. *Secretary,* Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Louis G. Fournier. *Secretary,* Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Charles D. Kimball. *Secretary-Treasurer,* Robert K. Plant, 732 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.

Denver Gynecological and Obstetrical Society. (1942) *President,* Edward L. Harvey. *Secretary-Treasurer,* Jack M. Simmons, Jr., 804 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Benj. E. Urdan, Milwaukee. *Secretary-Treasurer,* Christine F. Helm, 2212 Rowley Ave., Madison 5, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* D. Dalton Deeds. *Secretary,* Jesse A. Rust, Jr., 3115 University Ave., San Diego 4, Calif. Meetings held on the last Friday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* H. A. Wheeler, Grand Forks. *Secretary,* C. B. Darner, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Walter McMann. *Secretary-Treasurer,* L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.

Columbus Obstetric and Gynecologic Society. (1944) *President,* Wayne Brehm. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Robert S. Millen. *Secretary-Treasurer.* Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Charles W. Frank. *Secretary,* Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Harold V. Holter. *Secretary,* William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* A. M. McCausland. *Secretary-Treasurer,* Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Bradford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* H. B. Atlee. *Secretary,* K. M. Grant. Annual meeting, June, 1950.

Akron Obstetrical and Gynecological Society. (1946) *President,* H. H. Gibson. *Secretary-Treasurer,* E. A. Reimenschneider, Second National Bldg., Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.

Minnesota Obstetrical and Gynecological Society. *President,* Russell J. Moe. *Secretary,* John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President*, Ralph Luikhart. *Secretary-Treasurer*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President*, John W. Records. *Secretary-Treasurer*, Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.

Cleveland Obstetrical and Gynecological Society. (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

New Jersey Obstetrical and Gynecological Society. (1947) *President*, George B. German. *Secretary*, C. Norman Witte, Pt. Pleasant, N. J. Meetings semiannually.

Honolulu Obstetrical and Gynecological Society. (1947) *President*, K. S. Tom. *Secretary*, S. Nishijima, 1221 Victoria St., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.

Oregon Society of Obstetricians and Gynecologists. *President*, Gerald Kinzel. *Secretary-Treasurer*, Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.

National Federation of Obstetric-Gynecologic Societies. (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.

Dayton Obstetrical and Gynecological Society. (1937) *President*, Albert Hirsheimer. *Secretary*, Walter K. Gregg, Dayton, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.

Queens Gynecological Society. (1948) *President*, Edward C. Veprovsky. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.

Mississippi Association of Obstetricians and Gynecologists. (1947) *President*, R. A. Street, Jr. *Secretary*, William Weiner, Barnett-Madden Bldg., Jackson, Miss. Meetings held semiannually.

Florida Obstetrical and Gynecological Society. *President*, Charles J. Collins. *Secretary*, Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.

South Carolina Obstetrical and Gynecological Society. (1946) *President*, J. Decherd Guess. *Secretary*, Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.

Buffalo Obstetrical and Gynecological Society. (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.

El Paso Gynecological Society. (1948) *President*, Gerald H. Jordan. *Secretary-Treasurer*, Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.

Kentucky Obstetrical and Gynecological Society. (1947) *President*, A. J. Whitehouse. *Secretary*, Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.

Indianapolis Obstetrical and Gynecological Society. (1947) *President*, David L. Smith. *Secretary*, Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.

Houston Obstetrical and Gynecological Society. (1939) *President*, John A. Wall. *Secretary-Treasurer*, Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.

Iowa Obstetric and Gynecologic Society. *President*, J. H. Randall. *Secretary*, William C. Keettel, Iowa City, Iowa.

Memphis Obstetrical and Gynecological Society. (1950) *President*, James M. Brockman. *Secretary*, James H. Smith, 1195 Poplar Ave., Memphis 5, Tenn. Meetings, fourth Friday, October to May.